IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S) : Deborah C. Mash
SERIAL NO. : 09/486,613
FILED : February 29, 2000
FOR : Noribogaine in the Treatment of Pain and Drug Addiction
GROUP ART UNIT : 1617
Examiner : S.A. Jiang

MailDrop: Non-fee Amendment
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

Declaration of Dr. Deborah C. Mash

SIR:

1. I, Deborah C. Mash, declare as follows:

2. I am a citizen of the United States of America.

3. I am the sole inventor of the subject matter of the above-referenced patent application.

4. I have over 20 years experience as a Ph.D. level researcher in the pharmaceutical/biological sciences.

5. I am presently a Full Professor in the Department of Professor of Neurology and Molecular and Cellular Pharmacology, University of Miami School of Medicine, Miami, Florida, and have held that position since June, 1997.

6. Since 1996, I have been the Jeanne C. Levey Professor of Parkinson's Disease Research at the Universitiy of Miami, Miami, Florida.

7. Since, 1995, I have been a Member, Scientific Advisory Panel, Heffter Research Institute, Lafayette, Indiana.

8. Since 2000, I have been a Member, Scientific Advisory Board for Life Extension, Fort Lauderdale, Florida.

9. From 2000-2003, I was a a Member, National Institutes of Health, Brain Disorders & Clinical Neuroscience ZRG1 (BDCN-6).

10. In 2001, I was a Member, National Institutes of Health, Center of Biologic Research and Excellence (COBRE).

11. In 2002, I was a Visiting Scholar, Departments of Psychology and Biology, Victoria University, Wellington, New Zealand.

12. From 1991-1996, I was a Member, National Institutes of Health, NINDS-NSPA Program Project Review Committee A.

13. From 1991-1997, I was Associate Professor of Neurology and Pharmacology, University of Miami School of Medicine, Miami, Florida.

14. Since 1990, I have been Associate Director for Basic Research, Comprehensive Drug Research Center.

15. From 1986-1991, I was Assistant Professor of Neurology and Pharmacology, University of Miami School of Medicine, Miami, Florida.

16. From 1984-1986, I was a Postdoctoral Fellow in Neurology (Neuroanatomy), Harvard Medical School, Boston, Massachussetts where I conducted human and primate

architectonic studies of cholinergic receptor subtypes under the direction of M-Marcel Mesulam, M.D.

17. From 1980-1984, I was a graduate student in pharmacology, University of Miami School of Medicine, Miami, Florida where my research was in biochemical and autoradiographic studies of muscarnic receptor subtypes in rat and human brain. In 1984, I received my Ph.D. in Pharmacology (Neuropharmacology) from the University of Miami School of Medicine, Miami, Florida. My dissertation was "Autoradiographic localization of M_2 muscarine receptors in the rat brain suggests a presynaptic location on cholinergic tracts: Implications for Alzheimer's disease".

18. In 1980, I received a M.S. degree in Pharmacology and Toxicology (Neuropharmacology) from the Florida A & M University, Tallahassee, Florida.

19. In 1975, I received a B.A degree (Cum Laude) in Experimental Psychology from Florida State University, Tallahassee, Florida.

20. My primary areas of technical expertise include the following:

- Neuropharmacology, especially brain neuropharmacology;
- Neurodegenerative disorders;
- Addictive disorders/addiction; and
- Opioid Pharmacology.

21. I have published over one hundred eighty (180) peer-reviewed articles, a number of which relate to ibogaine and neuribogaine, their pharmacological effects and metabolism of ibogaine to neuribogaine.

22. I have received numerous honors and awards including:

1980-84	NIH Predoctoral Traineeship
1984-86	NIH Postdoctoral Traineeship
1984	Upjohn Award. First Place Graduate Student Category

1984	Roche Laboratories Award in Clinical Sc: :nces
1984	James E. Beale II Aware in Neuroscience
1984	Boehringer Ingelheim Research Award
1996	Jeanne C. Levey Professor Neurology, Er lowed Chair
2002	Professional Leadership Award, National Parkinson's Foundation
2002	Alzheimer's Associate Medical Honoree

23. I am a member of numerous professional and h norary organizations including the Society for Neuroscience, Sigma Xi, International Brain Re earch Organization, American Association, New York Academy of Sciences, American A ademy of Neurology and the American Society for Pharmacology and Experimental The apeutics.

24. I am or have been an *ad hoc reviewer* of article in a number of scientific publications including Brain Research; Neurology; Journal f Neurochemistry; Neurobiology of Aging; Journal of Immunopharmacology; Journal of Neurc science, Pharmacology and Behavior; Life Sciences (Pharmacology Letters); European Journal of Pharmacology; Annals of Neurology; Neurology; Journal of Comparative Neurology; Synapse; Psychopharmacology; and the American College of Neuropsychopharmacology.

25. I am sole inventor of the subject matter of pater t application number serial number 09/486,613, entitled "Noribogaine in the Treatment of Pai and Drug Addiction". I am familiar with the subject matter presently claimed which is directed o the use of noribogaine as an opioid agonist (μ receptor agonist) in the treatment of pain as clain ed. I understand that my invention as set forth claims 6-9 and 25-30 of the response submitted with this declaration are directed to methods of treating pain in a patient with an opioid recepto agonist without addiction to the patient, the method comprising administering to the patient a pharmaceutical composition which consists essentially of an amount of noribogaine or its pha naceutically acceptable salt to reduce or eliminate pain in the patient (claims 25-30), or alternativ ly noribogaine in combination with an opioid antagonist to reduce or eliminate pain in the patie nt (claims 6-9).

26. I have read the Examiner's office action dated September 26, 2005 and understand that the Examiner, on pages 3-10, essentially has rejected the present invention by suggesting that my invention does not indicate the *type* of pain which is treated, and that the references cited against my invention, namely Olney, U.S. patent no. 5,925,634 ("Olney") teaches my invention alone or that my invention is obvious over the teachings of Olney combined with other references, namely GB 841,697 ("GB"697") in view of Hussain, U.S. patent no. 4,464,378 ("Hussain"). I respectfully disagree.

27. The present invention as claimed is directed to a method of treating pain with noribogaine, which is an opioid agonist. Thus, using noribogaine, a patient may be treated with an opioid agonist without the addiction normally associated with the administration of a traditional opioid agonist such as morphine. This was unexpected. I understand that the Examiner contends that the claims do not teach which *type* of pain is treated with noribogaine, but the activity of noribogaine is as an opioid agonist in the treatment of pain. Contrary to the Examiner's contention, opioid agonists in the first instance are primarily useful for treating nociceptive pain, i.e., pain which is mediated primarily through the μ receptor. Nociceptive pain is distinguishable from neuropathic pain, which is mediated through NMDA receptors. Thus, by using the term "opioid agonist" in the claims, it is understood that noribogaine can used in the same manner that morphine (and other opioid agonists) can be used, but without the corresponding addiction which occurs with opioid use.

28. I am familiar with the reference Olney and I do not believe that Olney teaches my invention. In the first instance, to the extent that Olney teaches the use of ibogaine for pain (a proposition which is, in the first instance, questionable, given the psychotropic or hallucinogenic side effects of ibogaine), that use is for *neuropathic pain mediated through NMDA receptors*, not nociceptive pain mediated through μ receptors as in the case of noribogaine. It is noted here that even Olney indicates that ibogaine is used for neuropathic pain, *i.e. pain which does not respond conventionally to opiate drugs such as morphine* (see Olney abstract and column 7, lines 17-19). That neuropathic pain does not conventionally respond to opiate drugs and was generally known in the art as failing to respond to opiod drugs is also supported by the following references:

Hanks, *British Medical Bulletin,* 47, 3, 718-731 (1991); Kuypers, et al., *Pain,* 47, 5-12 (1991); Cherny, et al., *Neurology,* 44, 857 (May, 1994); Martin and Hagan, *Journal of Pain Symptoms Management,* 14, 2, 99-117, (1997); Garcia and Altman, *Seminars in Arthritis and Rheumatism,* 27, 1, 1-16 (August, 1997); and Abstract, Shir, et al., *Harefuah,* 118, 8, 452-454 (1990), copies enclosed. It is noted that the art failed to recognize that ibogaine could be used to treat nociceptive pain (i.e., pain which can be treated with an opioid agonist) and obviously Olney does not teach such a method. Rather, Olney *at best* teaches that ibogaine may be used in certain circumstances to treat neuropathic pain which does not respond to an opioid agonist, because such neuropathic pain is mediated through a receptor (NMDA), upon which the opioid agonists were understood to be inactive. Thus, if Olney teaches anything, it is that ibogaine may be used to treat pain which does not conventionally respond to morphine and other opioid agonists, i.e., neuropathic pain which is mediated through NMDA receptors.

29. That ibogaine cannot be used to treat nociceptive pain in the same manner as morphine or noribogaine may be found in the present application in the examples on page 9-10. That example teaches that morphine and noribogaine are full μ-opioid receptor agonists (anti-nocicipetive agents), whereas ibogaine was essentially inactive in the assay (page 9). Thus, the experiment which is presented in the present application evidences that noribogaine is a full μ-opioid receptor agonist and has efficacy as an antinociceptive agent (page 9, line 21), whereas ibogaine clearly was not active and is not an antinociceptive agent. This experiment is consistent with the general understanding in the art that ibogaine does not exhibit μ-opioid receptor agonist activity and therefore, cannot be used as a substitute for morphine to treat nociceptive pain. From these experiments and a review of the art, a scientist would conclude that ibogaine is not useful for treating pain which responds to morphine (nociceptive pain).

30. Thus, ibogaine would not be used to treat nociceptive pain as a substitute for morphine because ibogaine does not have the type of activity (i.e., μ receptor agonist activity) consistent with the treatment of nociceptive pain. Prior to the present invention it was not known that noribogaine possessed μ receptor agonist activity and could be used as a substitute for morphine. Not only does noribogaine possess good antinociceptive (pain) activity, noribogaine

can be administered without the patient suffering from the withdrawal symptoms associated with morphine administration. This is clearly not taught by Olney. In fact, Olney teaches that the action of ibogaine and morphine are completely distinguishable because they treat different types of pain. The same is true for ibogaine and noribogaine.

31. When a patient is being treated for pain, the first agents which are used to treat pain are the antinociceptive opioid agonists. It is only after the opioid agonists are shown to be incompletely effective or ineffective that neuropathic pain is suspected and other agents are then used. Thus, in the first instance, ibogaine will never be used to treat nociceptive pain, based upon the teachings of Olney. Moreover, the experiment presented in the specification on pages 9-10 of the present application confirms Olney's teachings in this regard. Thus, pursuant to the teachings of Olney, Ibogaine may be used *alone* to treat neuropathic pain or in instances where the opioid agonists are incompletely effective, ibogaine may be combined with an opioid agonist to treat pain which has both antinociceptive and neuropathic attributes. But such a combination would only theoretically be used after initial use by the preferred agent, morphine. Thus, while the prior art anticipates the *possibility* of using ibogaine alone to treat neuropathic pain or ibogaine in combination with a traditional opioid agonist to treat pain having both neuropathic and nociceptive components, in practice opioids will invariably be used as the first step in the treatment of pain. Nonetheless, the present invention clearly distinguishes over both of these methods. Indeed, the Hanks, reference, *ibid,* at page 719, lines 9-12 of third full paragraph, presupposes that opioid therapy will *invariably be part of the therapeutic regimen* in treating pain of mixed origin.

32. As a separate note it is acknowledged that ibogaine metabolizes to noribogaine, as well as other metabolites. However, the pharmacokinetics of this metabolism and the concentration or amount of noribogaine which will accumulate in a patient will vary widely depending on the patient's genetics and other drugs a patient may be taking. The level of activity and/or the amount of one or more isoforms of cytochrome l 450 present in the patient is reflective of the patient's genetics and about 5-10% or more of all patients may be characterized as poor metabolizers of ibogaine. In addition, other drugs/agents which a patient takes can

greatly influence the metabolism of ibogaine to noribogaine. In many instances, depending on the patient, that patient may be a poor metabolizer of ibogaine, or alternatively, other drugs the patient may be taking may substantially inhibit or influence the amount of noribogaine which will be produced from ibogaine during metabolism such that the amount of noribogaine is not always constant, known or substantial. Thus, even in the unlikely event that ibogaine was administered for treating neuropathic pain *alone*, such administration would not necessarily produce sufficient quantities of noribogaine to treat nociceptive pain, especially if that patient were a poor metabolizer or were taking other agents for the treatment of pain or other ailments. See, for example, Obach, et al., *Drug Metabol. Disp.*, 26, 8, 764-768 (1998) and Mash, et al., "Ibogaine in the treatment of heroin withdrawal." In: Ibogaine: Proceedings of the first International Conference., Alkaloid Series, Volume 56. Editors: Dr. K. Alper and Dr. S. Glick. Academic Press, San Diego, California pp 156-170, 2001, enclosed.

33. I further declare that all statements made herein of my own personal knowledge are rue and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12/21/05 _____

Deborah C. Mash

British Medical Bulletin (1991) Vol. 47, No. 3, pp. 718–731

B

Opioid-responsive and opioid-non-responsive pain in cancer

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Cancer pain in general responds in a predictable way to analgesic drugs and drug therapy is the mainstay of treatment, successfully controlling pain in 70–90% of patients. The two major problem areas are pain associated with nerve damage, and 'incident' (movement-related) bone pain. Nerve damage pain tends not to respond well to morphine or other opioids. The difficulty with severe incident pain is that if the dose of opioid is titrated sufficiently to relieve the pain on weight-bearing or on movement and is then given regularly at this level, it is too much for the patient at rest. The patient may then experience excessive side-effects at rest, but still have pain on movement. Other examples of pain which may be resistant to treatment with opioid analgesics are bladder and rectal tenesmus, pancreatic pain, and pain associated with decubitus ulcers or other superficial ulcers subjected to pressure or shearing forces. Management of non-opioid-responsive pain may include a variety of treatments involving adjuvant analgesic drugs and non-drug measures.

Most pain in cancer can be controlled using orally-administered analgesics and adjuvant drugs. It is reported that 70–90% of patients with cancer pain respond to pharmacological management[1–3] and this response may be sustained for months or years.[4] Such high response rates are not universally achieved and the main

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reasons for failure are inexperience and lack of knowledge of the simple principles of effective analgesic use (now being widely disseminated by the WHO[5]). It is relevant to keep this in mind in any discussion of so-called opioid-responsive and non-responsive pain. A proportion of apparently unresponsive pains merely require more effective use of the available drugs.

That said, there are a hard core of patients whose pain is not well controlled with opioid analgesics. The term opioid-non-responsive pain has been coined in recent years to describe this phenomenon. The term is not altogether satisfactory because it is too categorical, implying that a pain either **does** respond to opioid analgesics or **does not**. Rarely is there such a clear distinction in clinical practice with the latter group.

Another complication is that a pain may respond to opioid analgesics but may not be well managed by using the drugs in a conventional manner. 'Incident' (movement related) bone pain is the main example of this type of problem: if the dose of opioid is titrated sufficiently to control pain on movement and then given regularly at this level, it is too much for the patient at rest and will cause excessive side-effects.

Opioid-responsive and opioid-non-responsive pain are often equated with nociceptive and non-nociceptive pain, and in general this seems to be a valid rule of thumb as the basis for the differentiation.[6] Nociceptive pain responds to anti-nociceptive measures, which in pharmacological terms means analgesics. Non-nociceptive pain does not respond in a straightforward manner to analgesic drugs. Some hold that this is an absolute lack of response,[7] whilst others suggest that it is relative, and that if a sufficient dose of opioid is used at least a partial response will be obtained. This controversy is academic because clinically one is usually dealing with a mixed picture and this means that invariably an opioid analgesic will be part of the therapeutic regimen.

The clinical definition of opioid non-responsive pain embraces rather more than whether or not a pain is **sensitive** to opioid analgesics. It implies also a differential response in an individual, in which the patient does not derive adequate analgesia, but does experience other pharmacological actions of the opioid drug (as unwanted effects). Much rarer is the patient who does not experience any pharmacodynamic effect at appropriate therapeutic doses. Usually the balance between analgesia and unwanted effects produced by regular oral morphine weighs very much towards analge-

sia. Unwanted effects are in general easily managed without exceptional measures and are not dose-limiting.

Thus the distinction between opioid-responsive and opioid-non-responsive pain in cancer cannot be couched in precise terms. It encompasses the concept of **sensitivity** to treatment with opioid analgesics, but also implicit is the balance between analgesia and unwanted effects. A working definition is that opioid non-responsive pain is pain which is inadequately relieved by opioid analgesics given in a dose which causes intolerable side-effects despite routine measures to control them.

OPIOID-RESPONSIVE PAIN: CURRENT MANAGEMENT

Morphine is the strong opioid analgesic of choice used according to well-proven principles. It is given by mouth, the dose is tailored to the individual patient, doses are repeated so that the pain is prevented from returning, and there is no arbitrary upper limit.

Dose-titration

Morphine is available in three formulations for oral use: an elixir, a tablet (only recently introduced in the United Kingdom) and a controlled release tablet. (The first two are sometimes referred to as 'immediate or normal release' to distinguish them from the latter.)

An immediate-release formulation is preferable for dose titration. Peak plasma concentrations are achieved within the first hour with the elixir[8] but are slightly delayed with the standard tablet.[9] Both formulations give a rapid effect with a duration of about 4 hours. In contrast controlled release morphine tablets produce delayed peak plasma concentrations at 2–4 hours after administration, the peak is attenuated,[8] and the duration of effect is 12 hours. This means that with this preparation it is difficult both to assess the adequacy of analgesia in order to adjust the dose during the dose-finding period, and to make rapid dose changes.

Dose range

We have used doses of morphine elixir ranging from 2.5 mg 4-hourly to 2000 mg 4-hourly (and are aware of anecdotal reports of much higher doses). This range of almost a thousand-fold to achieve the same endpoint is remarkable and not seen in any other area of therapeutics.

Dose must be adjusted against effect, either until control of pain is achieved or side-effects become intolerable. The majority of patients will require 200 mg per day or less,[10–12] and very few will need high doses, but there is no definable maximum.

There is thus considerable inter-individual variation in the response to oral morphine. Some of the factors which contribute to this[13,14] are the severity of the pain, the type of pain, the affective components of pain, previous analgesic use, age and pharmacokinetic parameters. However, no complicated dose formula is necessary in order to determine the right dose for an individual patient. By titrating the dose against effect all of these factors will be taken into account. The simplest method of dose titration is to prescribe a four-hourly dose (based on previous analgesic use) and at the same time allow top-up doses of the same size for 'breakthrough' pain as frequently as necessary. After 24 or 48 hours the daily requirements may be reassessed and the regular 4-hourly dose adjusted as necessary.

Maintenance

Once a patient's morphine dose requirements have been determined, maintenance treatment will usually be with a controlled release tablet formulation. Most experience has been with a tablet designed for twice daily administration (MST Continus, MS Contin)[15] though others are now becoming available.

Patients with progressive disease and increasing pain may require continual adjustment of dose. For many patients, however, there is a period of stability during which dose requirements are unchanged or need only small adjustments.[4,16] Pharmacological tolerance appears to be rare, for reasons which we do not really understand. There are ample data to show that many patients may go for several months or sometimes years with little change in their morphine dosage.

Adverse effects

Constipation is an almost invariable adverse effect of morphine but should never be a reason for discontinuing the drug. It should be anticipated and treated prophylactically with adequate laxatives. Occasional patients do not become constipated.

Nausea and vomiting occurs in a half to two-thirds of patients taking oral morphine[17] but is variable in intensity and usually easy to control if it does develop. In many patients it is an initiation side-effect and may resolve with continued use of morphine. A small proportion of patients get severe nausea and vomiting which seems to be caused either by gastric stasis or increased vestibular sensitivity,[18] and which may occasionally prove intractable to treatment with conventional antiemetic drugs.

Sedation is frequent at the start of treatment but in the majority of patients resolves within a few days. Hallucinations and confusion are relatively unusual but may occur particularly in elderly patients, and once developed tend to persist unless the dose is reduced or the drug discontinued. This is the most likely adverse effect to necessitate a change in drug or route, though severe sedation or severe nausea and vomiting may also prompt such a move.

Our approach with intractable adverse effects is to change to an alternative strong opioid agonist, and we use phenazocine. This drug is methadone-related, has a longer duration of action of 6–8 hours, but is less flexible in dosage because it is only available as a 5 mg tablet (equivalent to 25 mg oral morphine). Often a change to phenazocine allows pain control to be achieved without the previously troublesome adverse effects associated with morphine.

If adverse effects persist we would move to spinal administration, preferably with intrathecal morphine. This is rare and has been necessary in less than 1% of our 450 admissions a year.

Adverse effects with oral morphine are more likely in the absence of pain. We have suggested that pain acts as a physiological antagonist of the CNS depressant effects of opioid analgesics[10] and that clinically this can be demonstrated in relation to respiratory depression.[19] McQuay has proposed that a possible explanation for this is that the respiratory centre in the medulla receives nociceptive input.[20,21] However, clinical experience suggests that this rule does not apply only to respiratory depression. It appears that a balance is usually achieved between nociceptive pain and the adverse effects of opioid analgesics, so that analgesia is achieved without intolerable unwanted symptoms. In the absence of such pain, adverse effects can become a major problem and such a development should prompt a re-evaluation of the patient.

This thesis is based on anecdotal clinical experience and requires more careful systematic documentation but if it is right it can explain a number of clinical observations.

Therapeutic failure with oral opioids

Non-opioid responsive pain will normally be defined by the development of intolerable adverse effects associated with inadequate analgesia. In this circumstance it is reasonable to ask three questions: 'If the opioid is administered by another route will efficacy (i.e. opioid-sensitivity) be improved?'; 'If the opioid is administered by another route will adverse effects be less?'; and 'Will an alternative oral opioid be either more effective or produce less side-effects?'

The subject of different routes of administration is discussed in detail elsewhere in this issue (*see* McQuay) but opinions remain divided. Most controversy surrounds the use of spinal administration and whether or not efficacy is enhanced by this route. There is no dispute that analgesia may be obtained with spinal opioids using much smaller doses, and that it has a longer duration, and (in the case particularly of intrathecal administration) is associated with a lesser incidence of systemic adverse effects. Some also suggest that the quality of analgesia is improved but a recent extensive review of published data suggests that, 'There is no conclusive evidence that opioids injected extradurally or intrathecally provide analgesia superior to that produced with other routes of administration.'[22]

Our approach is to use spinal administration of opioids in the management of a patient who has a demonstrably opioid-sensitive pain, but who develops intolerable side-effects with systemic administration of morphine or an alternative drug such as phenazocine.

There is no good evidence that efficacy is dependent on route of administration: in general, morphine has equal efficacy if given in appropriate dosage by oral, parenteral or spinal routes. There are always exceptions which prove the rule and there are certainly differences in dose requirements, speed of onset of action, duration of analgesia, and adverse effects which are dependent on the route of administration. However, if pain appears to be unresponsive to morphine by mouth, it is unlikely that changing the route will produce a response, unless there are obvious problems with absorption by the oral route in particular patients.

Alternatives to oral morphine

As indicated above we use phenazocine as our first alternative to oral morphine in patients unable to tolerate the latter drug. We do

not have quantitative data to present at this time to support this practice but our anecdotal experience is that frequently this manoeuvre works in achieving analgesia without disabling side-effects.

From time to time controversy has arisen over whether one opioid is more effective than another. There has for example in recent years been a long-running debate in several countries (particularly Canada and Australia) as to whether or not diamorphine is more effective than morphine. The evidence suggests that when relative potency is taken into account (i.e. using 'equianalgesic' doses) there is no difference in efficacy either between these two drugs, or between morphine and other strong opioids.

Opioid-irrelevant pain

In some patients the complaint of pain is more a reflection of social, psychological, or spiritual turmoil rather than a result of physical injury or damage. Such pain is not best treated with morphine and has been characterized as 'opioid-irrelevant pain' (by Hinton, quoted by Kearney[23]). Such pain may present as opioid-non-responsive pain. It may dominate a particular individual, or more commonly may form a component of many patients' complaint of pain. It needs always to be kept in mind.

OPIOID NON-RESPONSIVE PAIN

The two most difficult areas in cancer pain management are nerve damage pain and incident bone pain.[24] There are other cancer pain syndromes which respond poorly or not at all to opioid analgesics. These include bladder and rectal tenesmus, perineal pain associated with pelvic malignancy, pancreatic pain, and pain associated with decubitus ulcers or other superficial ulcers subjected to pressure or shearing forces.

Nerve damage pain

Nerves may be damaged by infiltration or compression by tumour, or as a result of viral infection, or by treatment with surgery, radiotherapy or chemotherapy. The resulting pain is often extremely difficult to treat.

The terminology here is confusing: neuralgia, neuropathic pain, neurogenic pain and deafferentation pain are all terms which are used interchangeably but may mean different things to different people. Neurogenic pain is discussed in detail elsewhere in this issue (*see* McMahon, Charlton, Devor, Wall, Bowsher) but several points are worthy of emphasis here.

Neuropathic pain appears to be relatively insensitive to opioids,[6] though as discussed above this is probably not an absolute phenomenon. Peripheral nerve lesions are often associated both with neuropathic pain and nerve trunk pain[25] which is likely to be responsive to opioids. Thus nerve damage is invariably associated with both nociceptive and non-nociceptive pain, and it is important that opioid analgesics are not automatically eschewed when a diagnosis of nerve pain is made. The usual step-wise approach and dose-titration of opioid should be employed, but at the same time alternative treatments may be required.

Nerve damage pain may include a sympathetic component and sympathetic blocks may be helpful.[26] In the management of the other components of neuropathic pain treatments should be targeted at specific symptoms:[27] hyperaesthesia and allodynia (pain due to a non-noxious stimulus); lancinating dysaesthesiae; and burning, crawling or compressing sensations. A variety of drug[28] and non-drug treatments[29] may need to be tried.

Corticosteroids are frequently not considered, yet may produce substantial improvement in neuropathic symptoms in cancer patients. Corticosteroids inhibit the production of prostaglandins and also by blocking the action of lipo-oxygenase, of leukotrienes. The reduction of inflammation, inflammatory oedema and hyperaemia surrounding a tumour mass may relieve the pressure on a nerve, or within a nerve bundle where there is infiltration by tumour. Corticosteroids may also reduce the abnormal sensitivity of nociceptive nerve endings resulting from inflammatory processes associated with a tumour or metastasis, and they have also been shown to reduce neuroma hyperexcitability.[30] Whatever the mechanism, useful palliation of symptoms is often achieved. An adequate dose of steroid is necessary in order to be sure not to miss a treatment effect (dexamethasone 4 mg bd or more).

On the basis of a similar rationale nonsteroidal antiinflammatory drugs may produce at least a partial response,[31] though corticosteroids are more predictable. If corticosteroids do alleviate symptoms and the mechanism is thought likely to be relief of nerve compression (for example radicular pain associated with vertebral metastases) treatment with radiotherapy should also be considered

since a longer-lasting effect may be obtained without steroid-related side-effects.

Psychotropic and anticonvulsant drugs, and other 'membrane-stabilizers' are discussed elsewhere. An important point to make here is that polypharmacy and iatrogenic problems are major deterrants to the use of these drugs in this patient population. Patients with nerve pain begin with the balance between unwanted drug effects and analgesia from conventional analgesics leaning towards unwanted effects. The addition of non-conventional analgesics with potent side-effect-producing potential may make a barely manageable situation quite impossible. These factors must be carefully weighed, and the application of antidepressants and anticonvulsants should perhaps be a little more cautious than is usual at present. Doses should start low and, as with morphine, there may be wide inter-individual variation in the therapeutic level which will be required. Thus the dose may need to be titrated through a considerable range for some patients.

The most recent addition to the armamentarium of membrane-stabilizers is the anti-arrythmic flecainide.[32] Our experience has been that a small number of patients with pain refractory to all other treatments have obtained substantial benefit from this drug. Caution and careful screening of patients is necessary because of its potential cardiotoxicity but the activity of flecainide in these particularly difficult pain states holds promise for future developments with this group of drugs.

Incident pain

Incident pain is a term most commonly applied to pain on weight-bearing or movement, but may also be caused by swallowing, micturition, defaecation, cough or some other action of the patient.[33] Frequently such 'breakthrough' pains can be adequately coped with by the use of a top-up dose of opioid, and invariably patients should have this made available to them. Our practice is to use the usual 4-hourly dose or equivalent, repeated as frequently as the breakthrough pain necessitates. It seems illogical to use a smaller dose though all sorts of formulae have been advocated.[33] There are no pharmacokinetic data to support one particular practice but our rationale is that the breakthrough dose should be adequate to relieve the breakthrough pain, and adverse effects are not a problem when our approach is adopted.

Much more difficult to manage is severe bone pain on movement

caused by skeletal metastases. The usual approach to management of radiotherapy[34] and morphine plus a non-steroidal antiinflammatory drug,[35] perhaps supplemented with a diphosphonate, will control most bone pain at rest. The dose of morphine should be titrated up to allow as much mobility as possible, but if the dose goes too high the patient is likely to experience excessive adverse effects at rest when there are no pain-provoking factors in play. This situation is not easily dealt with by using breakthrough doses of morphine because the movement-related pain is likely to be repetitive but unpredictable.

Alternative strategies are necessary. Orthopaedic intervention by pinning of long bones, spinal stabilization, or even joint replacement may be justified in order to enable an otherwise bed-bound patient to mobilize.[36] Obviously the prognosis and the general condition of the patient have to be carefully weighed but the benefit may be considerable. In patients for whom surgical intervention is not possible, external stabilization using splints or orthoses may be sufficient to allow mobilization without excruciating pain.

This is an area where the physiotherapy and occupational therapy members of the team have much to offer. The correct use of mobility aids, careful analysis and instruction of ergonomic principles, and adaptations of the patient's home environment are all likely to be more productive than continual pharmacological manipulation. These are difficult problems, sometimes inadequately managed in spite of all of the efforts of the multidisciplinary team. It is an important area for future research.

Pancreatic pain

The incidence of carcinoma of the pancreas has doubled in the UK in the last 40 years (and trebled in the USA) and is now the third most common site of cancer in the gastro-intestinal tract in men. Pain is common, occurring in up to 90% of patients at some stage, often at presentation.

Pain associated with carcinoma of the pancreas can frequently be problematical and occasionally appears to be quite unresponsive to opioid analgesics. Coeliac plexus block is often advocated for such pain[37,38] and indeed has been described as 'the best known and widely accepted nerve block for pain'.[3]

Two recent reviews draw somewhat different conclusions about the utility of this procedure. The first reports retrospectively on

extensive experience over a 4-year period in 101 patients: good pain relief was obtained in 80% of the patients with malignant disease (not all had carcinoma of the pancreas).[39]

However, a review of the literature on coeliac plexus block published over the last 25 years points out that the duration of analgesia, long-term morbidity and relative analgesic efficacy of coeliac plexus block are difficult to definitively categorise from the published papers and the authors question its usefulness.[40] However they also point out that in experienced hands it is a safe procedure.

There are certainly substantial data similar to that cited in the first review above, claiming high response rates with this technique. Our experience is that there are widely differing responses to this procedure in different patients. However, significant benefit is frequently obtained at the risk of minimal morbidity, and this is the crucial equation. We would continue to use this block in [illegible] not well controlled using oral opioids. There is a need for more rigorous evaluation of the technique and comparison with other methods of treatment. Some have suggested, for example, that epidural morphine may be more effective for pancreatic pain (Husebo, personal communication). This remains an open question.

Other opioid non-responsive pains

It is not uncommon to have a patient receiving large doses of opioid analgesics who still complains of severe discomfort from pressure sores. To some extent pressure sore pain is incident pain because it is most troublesome when the patient is lying on the affected area, or brushing against it. Drugs are not the mainstay of treatment. There is substantial literature on this subject and it is not appropriate to go into detail here. Prevention is the main concern[41] but once developed, pressure sores will require the use of special mattresses or beds and careful wound management. The usual approach to analgesia is to use a combination of an opioid with a non-steroidal antiinflammatory drug, but this is probably the least important measure in relieving pain caused by pressure sores.

Bladder and rectal tenesmus, and occasionally a proctalgia fugax-like severe episodic rectal spasm may complicate pelvic tumours and these spasmodic pains tend not to respond well to opioid analgesics, partly because of their intermittent nature. A

variety of pharmacological treatments are available and are usually tried with increasing desperation, but often to no avail. Simple solutions should be sought first. With bladder tenesmoid pains it is important to rule out infection or direct irritation by catheter, tumour, debris or blood clot. If none of these are present our approach to drugs would be to try first a non-steroidal antiinflammatory, and as second-line a smooth muscle relaxant such as flavoxate, dicyclomine or propantheline. Sedative phenothiazines, anxiolytic drugs and antidepressants have been advocated but we have not found them particularly helpful.

A recent paper reports impressive results in a small series of patients who underwent bilateral chemical lumbar sympathectomy for rectal tenesmoid pain.[42] About 80% (10 out of 12) of the patients achieved complete relief of pain. This is a safe technique associated with low morbidity and should certainly be kept in mind when faced with a [illegible] pain complaint.

Other pharmacological remedies have been advocated for non-malignant rectal spasm,[43] but this is another area which needs more research. It is important to recognize that current drug treatments may be ineffectual, and to avoid subjecting patients to endless changes in their drugs. A joint approach to management is required involving not just a consideration of pharmacological and nerve blocking measures but input from the whole multidisciplinary team. An alert, mobile patient with normal bowel function and taking a good diet is less likely to have intractable pain than if he were drowsy, bed-bound, constipated and miserable. Nursing, physiotherapy, occupational therapy and dietitian colleagues may all have an important role in the management of rectal spasm. Nerve blocks are covered in the last chapter (Wells & Miles) of this issue.

CONCLUSION

Most pain in cancer should be easily relieved because it responds in a predictable way to opioid analgesic drugs. Pain which does not respond so well can usually be at least ameliorated by the judicious use of adjuvant analgesics, non-drug measures, and the active involvement of the multidisciplinary team.

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Clinical Section

Morphine differentially affects the sens ory and affective pain ratings in neurogenic and idiopath ic forms of pain

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(Received 9 January 1991, revision received 20 Jun- 1991, accepted 21 June 1991)

Summary In a double-blind, placebo controlled crossover s udy, the effect of morphine on the affective and sensory pain ratings in different forms of chronic pain was i vestigated. Six patients suffering from central neurogenic pain, 8 from peripheral neurogenic pain and 6 from id opathic pain participated in the study. Morphine (mg/kg bodyweight) and placebo (saline) were administere l intravenously. Both the affective and sensory dimensions of pain sensation were assessed by means of the 101 point rating scale. From our results it appeared that morphine reduced the affective but not the sensory dimensic n of pain sensation in both groups of neurogenic pain patients. In the idiopathic pain group, neither the affective n or the sensory dimension of pain sensation were affected. The observed differences in opioid responsiveness w re neither the result of differences in opioid consumption nor of differences in baseline pain levels.

Keywords: Morphine; Analgesia; Pain sensory ratings; Pain affec ratings; Neurogenic pain; Idiopathic pain

Introduction

The question of whether opioids relieve neurogenic pain remains 'an apple of discord' in the area of pain treatment. Few topics in pain research are so emotion-charged as this one [11,15,23]. It divides both researchers and clinicians in two almost mutually exclusive camps; those of the strong protagonists of the use of opioids in neurogenic pain [3,14,15,19,21] and those of antagonists [1,2,18,20]. Since very few controlled studies have taken place in which the question 'do opioids relieve neurogenic pain?' has been thoroughly discussed, the arguments on both sides are based on limited personal experience, emotional attitudes or uncontrolled case reports rather than on firm scientific evidence.

One of the few studies in which the question of opioid sensitivity of neurogenic pain was systematically addressed, is that by Arnér and Meyerson [1]. Although the paper received much criticism [3], it is one of the few placebo controlled explorations of this question. This study indicated that opioids fail to suppress neurogenic pain. However, in view of these results, it is difficult to explain why many neurogenic pain patients consume high doses of opioids for long periods [14,21]. Is it actually the case that, contrary to Arnér and Meyerson's finding, opioids do relieve neurogenic pain? We hypothesize that, in cases of neurogenic pain, opioids are primarily taken for their mood changing effects. Indeed, it has been well established that opioids do not only relieve pain but that they induce changes in mood as well [5,7,9,10,17].

Pain is a complex experience consisting not only of sensory but also of affective-motivational dimensions [12]. Hence, in the study of the action of analgesic drugs one should distinguish between pain as a specific 'sensation' and pain as 'suffering' [5]. The experimental design of Arnér and Meyerson's study did not address the issue of whether opioids differentially affect both dimensions. Therefore, the aim of the present study was to investigate the effects of morphine on the sensory and affective dimensions of pain sensation in different forms of chronic pain. Except for the neuro-

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genic pain patients already mentioned, we also included in our study patients suffering from idiopathic pain. It has been claimed that just like neurogenic pain, idiopathic pain does not respond to opioids.

Methods

Subjects

Twenty patients (11 women and 9 men) all suffering neurogenic or idiopathic pain participated in this study. Their mean age was 47 ± 15 years, ranging from 18 to 78 years. Only 3 patients were older than 65 years. The large majority of them were inpatients staying in the pain clinic department for a pain treatment program. Patients were informed about the purpose of the study and they all gave informed consent. The protocol was approved by the Ethical Committee of the hospital where the study took place.

Great care was taken in the patient selection procedure. All possible candidates were seen by the three permanent staff members of the pain clinic department, i.e., an anesthetist, a neurosurgeon and a psychiatrist. Whenever there was disagreement between the opinions of the staff members on the exact diagnosis of a patient, it was decided to withdraw the patient from participation. Patients in which no straightforward diagnosis could be assessed, as well as patients with a mixed pain pathology, were also withheld from participation. Another important issue in patient selection was their previous experience with opioids. Since it was impossible to exclude all patients who had ever taken opioid drugs (although strictly legalized and controlled by the Ministery of Health, the prescription of opioids for therapeutic purposes is relative permissive in Belgium), a more realistic criterion had to be adopted. Hence it was decided to exclude all patients showing signs of narcotic dependence or with a 'high' and regular daily opioid consumption. We are fully aware that this is a rather flexible and debatable criterion.

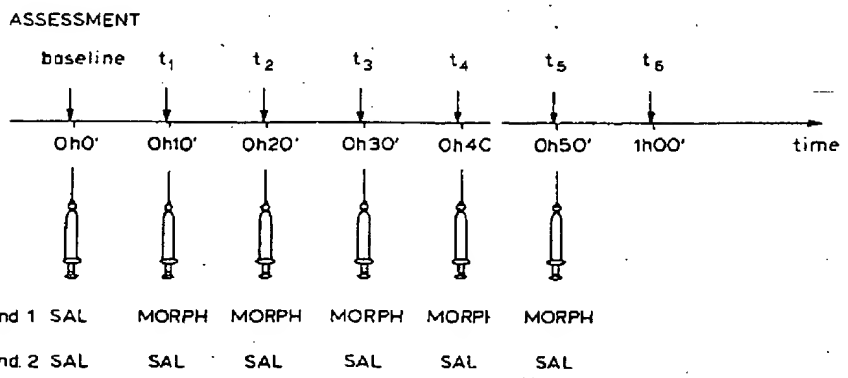
Description of the diagnostic categories

We largely adopted the classification as proposed by the IASP committee on pain taxonomy [13]. Furthermore, we made a distinction between central and peripheral neurogenic pain [see ref. 4, p. 3]: *central neurogenic pain* is pain associated with primary injury of the nervous system at the level of the brain or spinal cord; *peripheral neurogenic pain* is pain associated with primary injury of the peripheral nervous tissue; and *idiopathic pain* is pain in the absence of any obvious organic pathology. Usually, in these patients the pain complaints can be related with important psychodynamic problems or with traumatic (painful) life events.

Study procedure

A double-blind crossover design was used. Patient candidates were withheld from analgesics. At least had to elapse between the last analgesic medication and the start of the study. Patients were taught the differentiate between the affective and sensory dimensions of pain sensation. For this purpose, they were told a standard story in which the difference between both dimensions was highlighted. In addition the adjectives of the Dutch version of the McGill Pain Questionnaire [22] were used. When the patient was able to make this distinction, baseline measurements of both dimensions were made. Assessments were made by means of the 101-point rating scale [6]. In this scale patients were asked to rate their pain intensity or affect by giving a number between 0 and 100, with 0 indicating no pain and 100 the worst imaginable pain. The endpoints were anchored by verbal descriptors of both dimensions (e.g., the most imaginable unpleasant/intense sensation). The reason why we opted for this test instead of the traditionally used VAS was twofold. First, in comparison with the VAS, the 101-point rating scale has some practical advantages; it is extremely simple to administer and can be assessed verbally. Second, the use of VAS scales is not recommended in older patients [6]. After baseline assessments were made, patients either received morphine or a placebo (saline). Before administration of either drug, the patients were told the following: 'you will receive a drug and as a consequence, your pain can increase, decrease or remain unchanged'. Half of the patients first received morphine and then placebo, the other half first placebo and then morphine. The time interval between the two test sessions was at least 24 h. All drugs were administered intravenously by a third person. Both the patient and the clinician who made the assessments were not told which of the two drugs was being given. The patient received a total dose of morphine of 0.2 mg/kg bodyweight (hence a person of 70 kg received 14 mg morphine). This dose was administered gradually. Every 10 min the patient received a bolus injection of one fifth of the total dose. In total, 5 doses were administered. The method of administration was so arranged that, except for the first injection, patients were not aware that any injection had been given via the intravenous catheter. Assessments took place 10 min after the first injection and were repeated every 10 min up to 60 min. In order to maximize blindness and to eliminate as many primacy effects as possible, the intravenous administration was always saline, also in the placebo trials in the morphine conditions. Fig. 1 gives a schematic representation of the test procedure.

In order to test the reliability of the morphine effects, some patients underwent twice the morphine test and between-session correlations were calculated.



Schematic representation of the experimental procedure. As well in the placebo as in the morphine condition, the first injection was saline. The total dose of morphine (0.3 mg/kg) was divided over 5 injections; every 10 min, patients received one fifth of the total dose of morphine (bolus injections). t1, t2, ···, t6 refer to the consecutive assessments. All patients underwent both conditions.

...tical analysis

...Data were analyzed for all groups separately, by means of two-way analysis of variance, examining jointly ...treatment and time of measurement. Individual ...parisons between morphine and placebo scores ...between pre- and post-injection ratings were calculated by means of the paired Student's t test. Correlations between repeated morphine administrations were calculated by means of the Pearson product–moment correlation coefficient. Values of $P < 0.05$ were considered as statistically significant.

...sults

...Six patients suffering from central neurogenic pain, ...om peripheral neurogenic pain and 6 from idiopath... pain participated in the study. Details on the patie...its' age, sex, pain duration, pain description and medi...ation can be found in Tables I–III.

Th...ree patients suffering from central neurogenic and ... suffering from peripheral neurogenic pain previously took opioids. In most cases, the opioid drug was the ...ixed agonist/antagonist Valtran® (tilidine + nalo...one in a ratio 12.5:1). Tilidine belongs to the grou... of the weaker opioids; on a milligram basis, it is 22 ti...es less potent than morphine and the duration of its ac...tion is 4–6 h. Most patients declared that their pain ...was not relieved by these drugs. Only 2 of the neuro...genic pain patients occasionally had taken morphine per os: patient G.C. in the central neurogenic pain ...roup (very sporadically) with only moderate success ...nd patient V.J. in the peripheral neurogenic pain grou..., who stated that it had a good pain relieving

...BLE I

...RAL NEUROGENIC PAIN

...graphic data on the patients suffering central neurogenic pain (n = 6).

	Sex	Age	Diagnosis	Pain duration (years)	Pain de...cription/area	Medication
	F	54	C.V.A.	10	severe ...ain/left part of the body	tricyclic antidepressants
	F	53	thalamic pain	10	continu...us severe pain/ right ...art of the body	neuroleptics NSAIDs
	F	48	thalamic pain	5	continu...us severe pricking pain/ right ...art of the body	benzodiazepines tricyclic antidepressants
	M	43	paraplegic pain (section spinal cord T12-L1)	5	burning ...shooting pain/left leg	Valtran (80 drops/day) [a] baclofen (i.t.)
	F	65	thalamic pain	5	continu...us severe burning pain/ right ...art of the body	Valtran (120 drops/day) [a] non-opioid analgesics clonidine benzodiazepines
	M	55	medullary lesion	4	burning ...pricking pain/ T9–T...10 allodynia on touch ...dysesthesiae	Valtran (200 drops/day) [a] NSAIDs morphine p.o. [b]

...ed opioid agonist/antagonist of moderate potency; 20 drops Valtran® = 50 ...ng tilidine + 4 mg naloxone.

...possible to give an exact daily dose since patient only sporadically used it.

TABLE II

PERIPHERAL NEUROGENIC PAIN

Idiographic data on the patients suffering peripheral neurogenic pain (n = 8).

Patient	Sex	Age	Diagnosis	Pain duration (years)	Pain description/area	Medication
O.J.	F	48	cauda equina	< 1	burning pain/lumbosacral	tricyclic antidepressants non-opioid analgesics
V.J.	M	44	anesth. dolorosa V2 left	22	burning pain/left part of the face	carbamazepine Valtran® (100 drops/day)
P.A.	F	68	atypical trigeminal neuralgia	10	continuous gnawing pain/ right part of the face	morphine p.o. [b] carbamazepine benzodiazepines
L.D.	F	36	failed back surgery	5	lumbar pain/L5–S1 irradiating to both legs	analg/anti-pyeretics benzodiazepines analg/anti-pyeretics
V.N.	F	53	brachial plexus lesion	15	burning pain/right hand	Valtran® (20 drops/day) neuroleptics tricyclic antidepressants
V.M.	M	52	failed back surgery	12	burning pain/L5–S1 right	Valtran® (30 drops/day) benzodiazepines
J.H.	M	78	post-herpetic neuralgia	3	continuous burning pain/left T5–T10	tricyclic antidepressants Palfium 30 mg/day [c] benzodiazepines NSAIDs
L.N.	F	63	brachial plexus avulsion	4	pricking burning pain/ right arm and armpit	tricyclic antidepressants benzodiazepines analg/anti-pyeretics NSAIDs

[a] Mixed opioid agonist/antagonist of moderate potency; 20 drops Valtran® = 50 mg tilidine + 4 mg naloxone.
[b] Impossible to give an exact daily dose since patient only sporadically used it.
[c] Dextromoramide (pure opioid agonist).

effect. One patient in the peripheral neurogenic pain group claimed that his pain was relieved by the opioid dextromoramide, a μ opioid agonist which is perorally abou as potent as morphine. In the idiopathic p group there was only 1 patient who previously opioi ls. Mean pain duration was 6.5 years (range

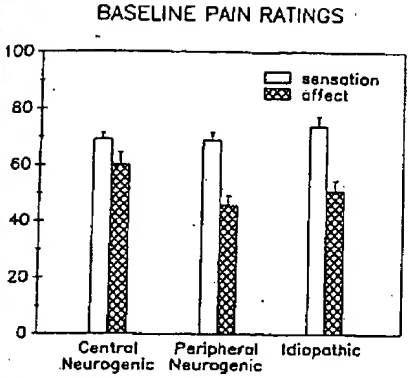
TABLE III

IDIOPATHIC PAIN

Idiographic data on the patients suffering idiopathic pain (n = 6).

Patient	Sex	Age	Diagnosis	Pain duration (years)	Pain description/area	Medication
V.W.	M	34	hypochondric personality	2	low lumba pain and cramp-like pain/ neck, ar s and chest	tricyclic antidepressants
D.F.	F	18	regressive-depressive syndrome	1	atypical co tinuous pricking pain/ under le breast	tricyclic antidepressants NSAIDs
D.I.	M	28	hysteric personality	11	atypical th acic pain	Valtran® (20 drops/day) tricyclic antidepressants
G.M.	F	36	hysteric personality	1	continuous low back pain irradiati to right leg	benzodiazepines non-opioid analgesics
B.G.	M	31	hypochondric personality	2	itching pai around chin	neuroleptics [b] tricyclic antidepressants NSAIDs
P.A.	M	27	hysteric personality	4	diffusely lo ilized pricking pain/ left shoul er and back	carbamazepine benzodiazepines carbamazepine

[a] Mixed opioid agonist/antagonist of moderate potency; 20 drops Valtran® = 50 m tilidine + 4 mg naloxone.
[b] Before his hospitalization, this patient took altogether 19 different medications to treat this pain.

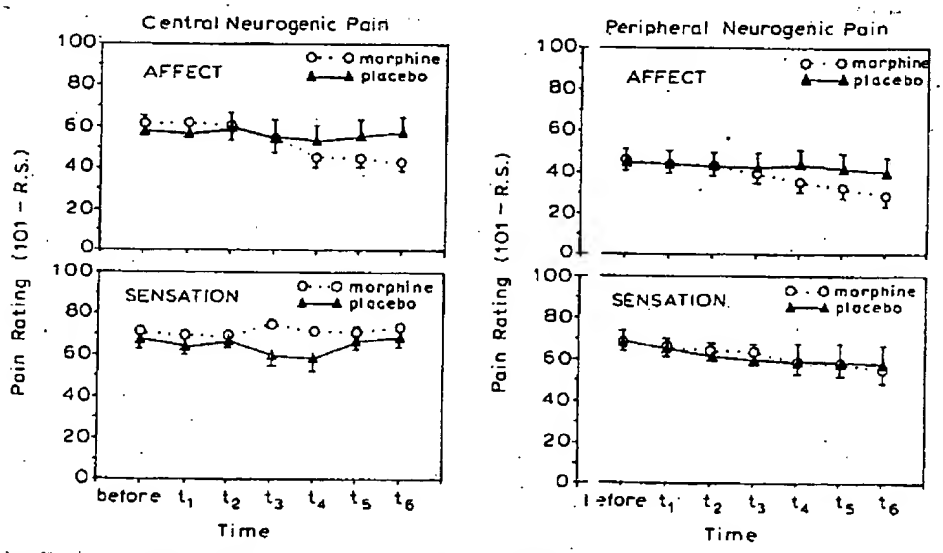


Baseline pain assessments in the 3 groups (mean + S.E.). As seen, initial pain sensory levels were remarkably similar; in groups values fluctuated around 70 on the 101-point rating In contradistinction, differences in baseline pain affect ratings the 3 groups were observed; highest pain affect ratings were obtained in the central neurogenic pain group.

in the central neurogenic pain group, 9 years < 1–22 years) in the peripheral neurogenic group and 3.5 years (range: 1–11 years) in the opathic pain group.

2 shows the mean initial sensory and affective ratings in the 3 groups. As can be seen, pain ory ratings were remarkably similar; in the 3 groups, ues fluctuated around 70 on the 101-point rating On the contrary, pain affect ratings differed in groups: the highest affect ratings were obtained central neurogenic pain group (60 points). The affect atings in the idiopathic and peripheral central pain g oups were clearly lower, respectively 50.7 and 45.5 p ints. In all groups, sensory ratings were higher than a fect ratings.

The effect of morphine on pain ratings in patients sufferi g central neurogenic pain is shown in the left part o Fig. 3. As shown in the upper left panel, in compa ison with placebo, morphine significantly reduced pain affect ratings ($F = 20, 36$; $P < 0.001$). Moreo er, there was a significant drug × time interaction ($F = 3,16$; $P < 0.05$). After morphine administration, p in affect ratings decreased from 62 (baseline) up to 3 at t6 on the 101-point rating scale. Placebo had no effect on pain affect ratings. When individual scores re compared, pain affect ratings were significantly ifferent at t4, t5 and t6. As shown in the lower left par of Fig. 3, pain sensory ratings were not decreased after morphine administration (there was even a trend towards increased sensory ratings). The results of the peripheral neurogenic pain group are shown in the righ part of Fig. 3. As can be seen in the upper right pa el, pain affect ratings after morphine administration were significantly lower than after placebo ($F = 21, 02$; $P < 0.001$). The mean pain affect ratings after morphine administration decreased from 45 (baselin) up to 28 at t6. Placebo had no effect on the affect s ores. When placebo and morphine scores are compar d, significant differences are observed at t4, t5 and t6. As shown in the lower right panel, pain sensory ratings i the two drug conditions did not differ significantly; here was a slight but non-significant decrease



3. Left part: pain affect and sensory ratings in central neurogenic pain patients ean + S.E.) after morphine and placebo administration = 6). In comparison with placebo, morphine significantly reduced the pain affec ratings ($F = 20, 36$; $P < 0.001$). Moreover, there was a ificant drug × time interaction ($F = 3, 16$; $P < 0.05$). In contradistinction, pain sens ry ratings were not decreased after morphine administration (there was even a trend towards increased pain sensory ratings). Right part: pain affect and sensory ratings in peripheral neurogenic pain ients (mean + S.E.) after morphine and placebo administration ($n = 8$). In compari n with placebo, morphine significantly reduced the pain affect ratings ($F = 21, 02$; $P < 0.001$). In both conditions, there was a slight bu non-significant decrease in pain sensory ratings.

after morphine as well as after placebo administration. Pain ratings decreased respectively from 68 up to 55 ($P > 0.5$) and from 69 up to 58 ($P > 0.5$). Looking at the individual results (data not shown), it appears that after morphine administration, pain sensory ratings were significantly decreased in 2 patients, namely from 90 to 20 (patient V.M.) and from 65 to 25 (patient L.N.). In these same patients, the administration of placebo produced a similar effect; pain sensory ratings decreased from 80 to 10 (V.M.) and from 70 to 50 (L.N.).

The results of the idiopathic pain group are shown in Fig. 4. Neither after administration of morphine nor after administration of placebo could any change in the pain affect (upper part) or pain sensory ratings (lower part) be observed.

Since in several patients more than one morphine test was performed, inter-session correlations could be calculated. Median inter-session correlations for pain affect ratings were high: $r = 0.95$ in the central neurogenic pain group (n = 3), $r = 0.86$ in the peripheral neurogenic pain group (n = 5) and $r = 0.82$ in the idiopathic pain group (n = 3). Due to the lack of variance in the pain sensory scores, no inter-session correlations for sensory ratings could be calculated.

In order to test whether the effect of morphine on pain ratings was co-determined by previous opioid exposure, we separately analyzed the results of opioid users and opioid naïves. To this purpose, the results of the patients from the 2 neurogenic pain groups were lumped together. As can be seen in Fig. 5, the mean

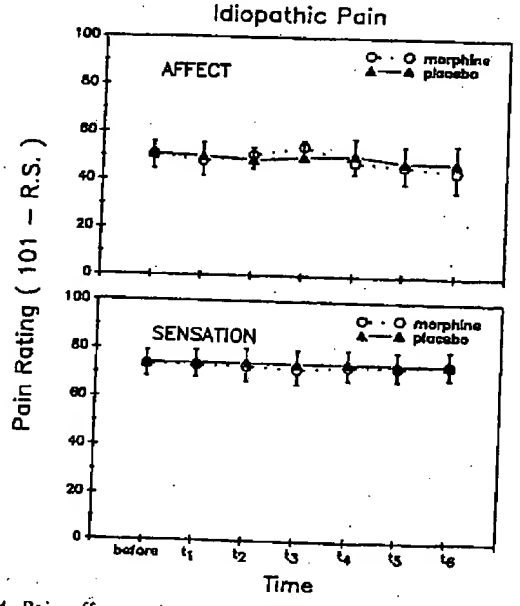


Fig. 4. Pain affect and sensory ratings in idiopathic pain patients (mean + S.E.) after morphine and placebo administration (n = 6). Morphine neither affected the affective nor the sensory pain ratings.

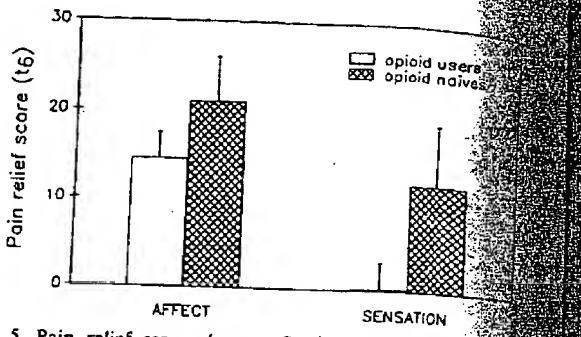


Fig. 5. Pain relief scores (mean + S.E.) at t6 in opioid users and opioid naïve patients suffering central or peripheral neurogenic pain (n = 14). As can be seen, there were no significant differences between opioid users and opioid naïves in mean pain affect relief ($t = 1.17$; $P > 0.05$) or pain sensory relief scores ($t = 1.47$; $P > 0.05$).

pain affect relief score at t6 in opioid users (n = 7) and opioid naïves (n = 7) was not significantly different ($t = 1.17$; $P > 0.05$ unpaired t test). The same was observed for the pain sensation scores ($t = 1.47$; $P > 0.05$ unpaired t test). The (non-significant) higher pain sensory relief scores in the opioid naïves is completely attributable to the results of patients V.M. and L.N. (vide supra).

Discussion

The aim of the present study was to assess the effects of morphine on the sensory and affective dimensions of pain sensation in different categories of chronic pain. The most intriguing finding of this study is certainly that morphine affected the affective but not the sensory dimension of pain sensation in patients suffering neurogenic pain. Whereas morphine dose dependently reduced the pain affect scores in the neurogenic pain groups, no effect was observed on the pain sensory ratings. This finding may offer a possible explanation for the contradictionary results in the literature on the effectiveness of opioids in the treatment of neurogenic pain. It may also give an answer to the question why most of the patients suffering neurogenic pain keep on taking opioids albeit that they admit that these drugs do not relieve their pains. Simply stated, the answer is that they do so, not because they feel less pain, but because they care less about it. The observed lack of effect on pain sensory ratings is in agreement with the findings by Arnér and Meyerson [1]. Although these authors did not explicitly make the distinction between affective and sensory pain ratings, they asked their subjects 'to concentrate on the effect of the pain and only afterwards to disregard feelings with a secondary, beneficial effect.' Thus, they probably measured sensory effects of opioids.

Comparing the results in our 2 neurogenic pain groups, it appears that pain affect scores were reduced to the same extent in both groups. In the central and peripheral neurogenic pain groups, scores decreased, respectively, by 19 and 17 points. Comparing the pain sensory scores, there was a slight difference between the results in both neurogenic pain groups. In the peripheral neurogenic pain group, there was a trend towards reduced pain sensory ratings, after morphine as well as after placebo administration. A similar trend was not found in the central neurogenic pain group. Looking at the individual data (not shown), it appears that this decrease can nearly completely be attributed to the results of patients V.M. and L.N. In both patients, sensory ratings decreased significantly, after morphine as well as after placebo administration. This raises the question whether the decrease in pain sensory ratings in these 2 patients after administration of morphine is a real opioid or rather a placebo effect. There are some arguments in favor of the placebo interpretation. First, only the placebo responders in each group responded to morphine. Second, these 2 patients were the only ones of the neurogenic pain group who already reported pain relief at t1, i.e., even before morphine was administered. These arguments certainly do not definitively rule out the morphine misinterpretation but, in any case, the results demonstrate the importance of a control condition in which no active substance is administered. Without the placebo condition, one could erroneously have concluded that opioids do suppress pain sensory ratings in peripheral neurogenic pain.

In the study by Arnér and Meyerson, it was shown that opioids fail to suppress idiopathic forms of pain. Looking at Fig. 4, our results seem to confirm and extend this conclusion: neither the sensory nor affective dimensions of pain sensation were reduced by morphine. The observation that morphine exerted no effect on pain affect ratings is rather surprising. In this study, idiopathic pain patients were the only ones who did not report pain affect relief after morphine administration. The fact that, in contradistinction with the other groups, most of them were opioid naïve might be put forward to explain this. However, in view of our finding that in the neurogenic pain group no significant differences in pain affect relief scores were found between opioid users and opioid naïves, this explanation seems difficult to hold.

How to explain the observed differences in opioid responsiveness in the 3 groups? The answer to this question largely remains to be elucidated and, for a discussion of this issue, we refer to the paper by Arnér and Meyerson [1]. In any case, the observed differences in opioid responsiveness are certainly not a consequence of differences in baseline pain levels. As is shown in Fig. 2, baseline measurements of pain sensory ratings were remarkably similar. In the 3 groups, scores ranged around 70 points on the 101-point rating scale, which corresponds with rather severe pain. In contradistinction, there were some differences between the pain affect ratings in the 3 groups. Highest baseline affect ratings were found in the central neurogenic pain group. This further confirms that the emotional-affective pain dimension is not simply a reflection of the sensory pain intensity but that it depends as well on psychological factors inherent to the pain syndrome [8,12,16].

The study by Arnér and Meyerson has been criticized for biased patient selection, since their neurogenic pain patients all had previously undergone unsuccessful opioid treatment. Our results demonstrate that even in opioid naïve persons, no effect of morphine on pain sensory ratings could be observed. In the 2 neurogenic pain groups, about half of the patients were opioid naïve. No significant differences in pain sensory ratings between them and previous opioid users were found. Moreover, the 2 neurogenic patients who claimed that they experienced pain relief by taking opioids (patients V.J. and J.H.) failed to show a significant effect on pain sensory ratings in our study. One might hypothesize that the patients who previously took opioids were in a state of withdrawal at the moment of the study and hence that the observed effects of morphine mainly reflect the treatment of this withdrawal syndrome. If this would be the case, opioid effects would only be expected in previous opioid users. As can be seen in Fig. 5, the degree of pain relief in opioid users and opioid naïve persons was not significantly different (there was even a trend towards higher pain relief scores in opioid naïve persons). Furthermore the fact that the 2 neurogenic pain patients in our study who reported pain relief after morphine were opioid naïve persons is also difficult to reconcile with the withdrawal interpretation. These considerations also make it improbable that in opioid naïve persons, dysphoria might have counteracted an analgesic effect.

It might be argued that our study population is too small to allow us to make firm conclusions on the opioid responsiveness of neurogenic pain. For several reasons, this critique does not seem to be justified. First, 14 patients suffering neurogenic pain participated in the study. Second, in 3 patients suffering from central and 5 suffering from peripheral neurogenic pain, the morphine test was performed twice. High inter-session correlations were observed which offers additional support for the reliability of our results.

To end we would like to warn against clinical overinterpretation of our results. It would be presumptuous to claim that on the basis of these results, a definitive answer can be given to the clinically relevant question

of whether opioids suppress pain of neurogenic origin. However, our results certainly add a new element in this complex and controversial debate.

Acknowledgements

The authors are grately indebted to Ms. Gilliams, Mrs. Feytons-Heeren and Mr. De Sutter for their expert secretarial and technical assistance.

This work was in part supported by the N.F.W.O. Grant No.. 3.0031.87 of Belgium and by Medtronic Belgium.

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Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms:

A combined analysis of controlled, single-dose studies

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Article abstract—We performed a combined analysis of the results from four controlled single-dose relative-potency studies to assess the impact of inferred pain mechanism on the response to an opioid drug. A total of 168 patients received 474 administrations of either morphine or heroin, and we assessed the analgesic response during a 6-hour period with visual analog scales. We summarized this as a total pain relief (TOTPAR) score. Two experienced pain clinicians reviewed information about pain characteristics and designated each case according to the inferred pain mechanism (neuropathic, nociceptive, or mixed) and the degree of confidence in the inferred mechanism (definite versus probable/possible). They grouped the cases as follows: nociceptive pain only (n = 205), neuropathic pain only (n = 49), and mixed (n = 220). We compared pain relief achieved by patients with different mechanisms, with TOTPAR adjusted for significant covariates (duration of prior opioid administration, doses of opioid administered in the previous 48 hours, pain intensity at the start of the study, BUN:creatinine ratio, and dose of administered opioid). The adjusted mean TOTPAR score of the group with any neuropathic pain was significantly lower than that of the group with nociceptive pain only (26.1 versus 20.4, $p = 0.02$). The score of the group with definite nociceptive pain alone (adjusted mean TOTPAR = 28.0) was significantly higher than scores of the groups with possible/probable nociceptive pain (TOTPAR = 19.9), mixed mechanisms (TOTPAR = 20.2), definite neuropathic pain alone (TOTPAR = 20.6), and possible/probable neuropathic pain alone (TOTPAR = 22.9). In pairwise comparisons, there were no significant differences in the adjusted mean TOTPAR scores among the latter four groups. Among the patients with neuropathic pain, the dose-response relationship was significant. These data support the postulate that opioid responsiveness is a continuum with extensive overlap in the responsiveness of pains mediated by neuropathic, nociceptive, and mixed pain mechanisms.

NEUROLOGY 1994;44:857-861

The clinical literature commonly describes pains as "nociceptive" or "neuropathic." The term "nociceptive pain" is applied when pain is perceived to be commensurate with tissue damage associated with an identifiable somatic or visceral lesion. "Neuropathic pain" is applied when pain is due to injury to, or diseases of, the peripheral or central neural structures or is perceived to be sustained by aberrant somatosensory processing at these sites.[1,2] These labels reflect inferences about underlying pathophysiology that cannot be independently confirmed and derive from the pain description, clinical signs, and evidence from ancillary tests. A neuropathic mechanism, for example, is most strongly suggested when a dysesthesia occurs in a region of motor, sensory, or autonomic dysfunction associated with a discrete nerve injury.[2] Although the distinctions implied by these labels have been questioned on the basis of experimental findings in animal models,[1] they are widely regarded as being clinically helpful.

One of the more salient issues related to the distinction between nociceptive and neuropathic pain is the continuing controversy regarding relative differences in opioid responsiveness.[3] Some clinicians have suggested that neuropathic pains may be inherently resistant to opioid analgesia,[4] whereas others have postulated that opioid responsiveness is a continuum and that neuropathic mechanisms may be one of the

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Supported by National Cancer Institute grant Ca32897.

Received August 11, 1993. Accepted for publication in final form November 4, 1993.

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Table 1. Distribution of study drug and dose administration in the four studies reviewed for this analysis

	IM morphine		IM heroin		PO heroin	
	8 mg	16 mg	4 mg	8 mg	20 mg	40 mg
Study 141*	64	59	61	57	—	—
Study 148†	—	—	10	8	8	—
Study 149†	—	—	14	14	15	16
Study 150†	—	—	48	—	46	54
Total number of administrations	64	59	133	79	69	70

IM Intramuscular.
PO Oral.
* Reported in part in Kniko et al.[5]
† Unpublished data.

factors associated with a diminished analgesic response.[5] Only a few controlled studies have evaluated the relationship between pain mechanism and opioid responsiveness, and the issue is not resolved.

We used a database drawn from the results of several double-blind, relative analgesic-potency assays carried out in cancer patients with chronic pain to assess the impact of inferred pain mechanism on the response to an opioid drug.

Methods. A combined analysis was performed on the data derived from four controlled, single-graded-dose analgesic studies conducted from 1978 to 1982 at Memorial Sloan-Kettering Cancer Center (table 1). The studies evaluated single intramuscular (IM) injections of morphine or heroin, single doses of oral (PO) heroin, and/or single doses of another study drug. Each study received approval from the Institutional Review Board of the institution, and all participating patients gave informed consent.

The studies used a twin crossover design in which patients were randomly assigned to receive either a high or low dose of a study drug.[6] There was a twofold difference in the low and high doses. All patients had chronic cancer-related pain that had been treated previously with an opioid regimen. The baseline opioid regimen was withheld prior to the test dose, which was administered when the patient reported the return of pain of moderate or greater severity. The test dose was administered using a double-blind technique. Following the dose, pain intensity and pain relief were measured repeatedly using visual analog scales (VAS) and categorical scales until 6 hours had elapsed or remedication was requested by the patient.

Patient information was prospectively recorded prior to administration of each test dose. These data included demographics, tumor type and extent of disease, pain descriptors, prior opioid treatment, and indicators of hepatic and renal function. For the present study, this information was supplemented by a record of the drug administered (morphine IM versus heroin IM versus heroin PO), the dose (high versus low), and the analgesic outcome. Analgesic outcome was recorded as the total pain relief (TOTPAR) summary score. TOTPAR was expressed as the percentage of maximal possible pain relief represented in the area under the curve describing changes in the VAS pain relief over time. The range of potential scores was 0 to 100.

Inferred pain mechanism. To classify cases according to inferred pain mechanisms, two experienced pain clinicians (N.I.C. and J.L.) independently reviewed the case records of each study patient. The pain mechanisms were labeled neuropathic or nociceptive and the degree of confidence in each inferred mechanism was graded as definite, probable, or possible. The criteria for the inference of a neuropathic mechanism included suggestive pain qualities (eg, lancinating, burning, or associated paresthesia or allodynia), distribution of pain consistent with neural damage (eg, radicular, polyradicular, or glove and stocking), and evidence of corresponding neural injury or disease. The criteria for the inference of a nociceptive mechanism included suggestive pain qualities (eg, aching, throbbing, colicky, or pulling), local or referred distribution of pain consistent with known patterns of visceral or somatic pain syndromes, and evidence of corresponding somatic or visceral injury. Those cases in which both mechanisms were inferred were classified as mixed. When the classifications of the two independent evaluators differed, the cases were reviewed with a third investigator (R.K.P.), and disagreement was resolved by consensus. None of the evaluators was aware of the analgesic study outcomes for the patient at the time of this assessment.

For the purpose of analyzing analgesic outcomes, patients were grouped according to pain mechanism and the certainty with which mechanism was inferred. The following groups were evaluated: nociceptive pain only (definite, probable, or possible), neuropathic pain only (definite, probable, or possible), and mixed syndromes. For the primary comparison, the population was dichotomized into a group with nociceptive pain only and a second group with any neuropathic pain, pooling the neuropathic only and mixed mechanism cases).

Data analysis. Covariate analysis was performed to identify variables associated with increased TOTPAR. The following covariates were evaluated: duration of prior opioid administration; dose of opioid administered during the 48 hours before the study drug was administered; pain intensity at the start of the study; high versus low test dose; age; sex; drug and route; extent of disease; serum lactate dehydrogenase; alkaline phosphatase and bilirubin; the blood urea nitrogen (BUN) creatinine ratio, and inferred pain mechanism. Univariate significance levels were evaluated using Student's *t* test for dichotomous variables and correlation coefficients for ordinal data. For the multivariate analysis, the variables were selected for a predictive model by stepwise linear regression. Significance levels for the final model were assessed after transforming TOTPAR scores to more closely satisfy implicit statistical assumptions of normality and constant error variance. In a separate analysis, the "poolability" of the four trials also was tested by determining whether the mean TOTPAR associated with the low and high doses varied across the studies after adjustment for covariates and by comparing the log dose-response slopes between the studies.

For the primary analysis which compared the analgesic response of pains differing in mechanism, TOTPAR was first adjusted for the significant covariates. Specifically, the covariate regression equation was used to project each TOTPAR score to the value that would have been obtained had all covariates been at their sample mean value. This adjustment was made for all significant covariates except pain mechanism; dose was excluded only in those analyses that assessed dose response for each pain mechanism.

With TOTPAR adjusted for significant covariates, opioid responsiveness of pains caused by nociceptive, neuropathic, and mixed mechanisms were compared. The post hoc group comparisons were evaluated by the conservative Scheffé method for linear contrasts in the context of an analysis of covariance.[7] Initial scores were performed of certainty (definite probable/possible least reliable, was in subsequent ar The primary ana PAR scores of the that of the group analyses compare groups.

Results. *Demo* patients, 88 wo ceived 474 asse dian age was 5 mon tumor type unknown prima (n = 8), bladder overwhelming was either meta = 31). At the ti of moderate or equianalgesic d which use a rel morphine, the during the 48 h to 100 mg mor dian duration o and 6 months o

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covariance.[7] Initial analyses of the adjusted TOTPAR scores were performed to validate the stratification by level of certainty (definite versus probable versus possible). The probable/possible distinction, which was subjectively the least reliable, was not significant for any mechanism, and in subsequent analyses these subgroups were combined. The primary analysis compared the mean adjusted TOTPAR scores of the groups with nociceptive pain alone with that of the groups with any neuropathic pain. Secondary analyses compared the TOTPAR scores of the other subgroups.

Results. *Demographics.* The sample comprised 168 patients, 88 women and 80 men, who together received 474 assessable drug administrations. The median age was 52 (range, 20 to 79). The six most common tumor types were lung (n = 26), breast (n = 25), unknown primary (n = 10), sarcoma (n = 8), prostate (n = 8), bladder (n = 8), and esophagus (n = 8). The overwhelming majority of patients had disease that was either metastatic (n = 119) or locally advanced (n = 31). At the time of the study, all patients had pain of moderate or greater intensity. Based on standard equianalgesic doses for patients with chronic pain,[8] which use a relative potency ratio of 3:1 for PO to IM morphine, the median opioid analgesic consumption during the 48 hours prior to the study was equivalent to 100 mg morphine IM (range, 0 to 520). The median duration of prior opioid therapy was between 2 and 6 months on a categorical scale.

Test for poolability of data. Individual studies, as designated by drug and route of administration, did not differ significantly in the TOTPAR scores obtained for either the low or the high doses or in the log dose-response relationships. These results, combined with the commonality in study methodology, investigators, chronology, and setting, indicate that the response data from these studies can be analyzed together without the introduction of systematic bias.

Covariate analysis. Covariate analysis demonstrated that the following variables were associated with increased TOTPAR scores: short duration of prior opioid administration, low doses of opioid in the previous 48 hours, low pain intensity at the start of the study, elevated BUN:creatinine ratio, and higher dose of administered opioid. Covariates that were not multivariately correlated with analgesic response included age, sex, drug and route of administration, extent of disease, lactate dehydrogenase, alkaline phosphatase, and bilirubin (table 2).

Assessment of inferred pain mechanism. The two independent assessors concurred in the assessment of a neuropathic component in 72% of the pains subjected to test doses. Concordance in the assessment of a nociceptive component was 91%. For the overall classification (neuropathic versus nociceptive versus mixed), there was agreement in 65% of the cases, and disagreements were resolved by consensus.

Ninety percent (n = 425) of the test doses were administered to patients who had a nociceptive component to their pain. Of these, 205 were administered to patients with nociceptive pain only (definite n = 158, probable/possible n = 47), and 220 were administered to patients who also had coexistent neuropathic pain. A neuropathic mechanism was the only cause of pain at the time of study in 49 cases (definite n = 29, probable/possible n = 20). Thus, 59% of the test doses (n = 269) were administered to patients assessed as having a neuropathic component to the pain.

Table 2. Covariate analysis of factors determining opioid responsiveness

Covariate	Univariate correlation or *t* test	Covariate multiple regression
Opioid dose in previous 48 hours	<0.0001	<0.0001
Duration prior opioid administration	<0.0001	<0.0030
BUN:creatinine ratio	0.0003	<0.0039
Pain intensity at initiation of study	0.0001	0.0025
Opioid study dose: high vs low	NS	0.0291
Time since last dose	0.0007	NS
Age	0.0331	NS
Bilirubin	0.0845	NS
Inferred pain mechanism	0.0001	0.0007

NS = not significant ($p > 0.10$).

Drug/route, sex, extent of disease, lactate dehydrogenase, and alkaline phosphatase were not significant factors determining opioid responsiveness by either univariate or covariate analysis.

The groups were not balanced for covariates predictive of analgesic response (table 3). Of the patients with neuropathic pain alone (definite and possible/probable), relatively few had pain reported as severe or excruciating at the start of the study, and the median dose of opioid administered during the previous 48 hours was relatively low in the possible/probable subgroup.

Opioid response according to inferred pain pathophysiology. The adjusted mean TOTPAR score of the group with any neuropathic pain was significantly lower than that of the group with nociceptive pain only (20.4 versus 26.1, $p = 0.0009$). The adjusted mean TOTPAR score of the group with definite nociceptive pain alone (TOTPAR = 28.0) was significantly higher than that of the possible/probable designation for the same mechanism (TOTPAR = 19.9), mixed mechanisms (TOTPAR = 20.2), definite neuropathic pain alone (TOTPAR = 20.6), and possible/probable neuropathic pain alone (TOTPAR = 22.9) ($p = 0.002$). In pairwise comparisons, there were no significant differences in the adjusted mean TOTPAR scores among the groups with possible/probable nociceptive pain alone, mixed mechanisms, definite neuropathic pain alone, and possible/probable neuropathic pain alone. Patients with neuropathic pain demonstrated a significant difference in adjusted TOTPAR between the low-dose and the high-dose group.

Discussion. This analysis of the results of 474 opioid test doses from four randomized double-blinded,

Table 3. The distribution of covariates positively correlated with TOTPAR between the pain mechanism groups

	Definite neuropathic pain alone (N = 29)	Possible/probable neuropathic pain alone (N = 20)	Definite nociceptive pain alone (N = 158)	Possible/probable nociceptive pain alone (N = 47)	Mixed (N = 220)
Median prior opioid dose*	120	60	90	110	100
Median duration prior opioid administration (mo)	8	6	7	6	7
Median BUN:creatinine ratio	12.5	14	15	11	15
% Severe-excruciating pain intensity at the start of the study	14	5	20	21	33
% High-dose study opioid	48	35	44	40	45

* Expressed as equivalent mg dose in 48 hours prior to the study of intramuscular morphine.

graded-dose analgesic trials suggests a great overlap in the responsiveness of pains mediated by neuropathic, nociceptive, and mixed pain mechanisms. Neuropathic pains did respond to an opioid analgesic, but the response to a fixed dose was generally less than the response of a nociceptive pain to the same dose. This difference in responsiveness was most pronounced when an exclusively nociceptive mechanism could be inferred with a high level of certainty.

The validity of these conclusions depends on (1) the methodologic controls used during each of the analgesic studies, (2) the validity of a combined analysis, (3) the validity of the covariate analysis and the subsequent adjustment of the outcome measure for significant covariates, and (4) the validity of the pain pathophysiology classification and comparison. The methodology used for this analysis addressed each of these issues, as follows:

The controlled single-dose assay is a well-validated method for the assessment of analgesic efficacy.[6,9,10] Although the use of the TOTPAR as a summary score for analgesia can potentially confound duration of effect with magnitude of effect when comparing dissimilar drugs with differing duration of action,[9] there is a broad consensus supporting the utility of the TOTPAR score for comparison of analgesia between different doses of one analgesic or analgesics of similar duration of action.[11] Important methodologic controls employed in each of the studies included random assignment of dose, double-blinded administration, and the use of validated outcome measures.

As described previously, the methodology for each trial was identical, as were the investigators and clinical setting.[12] These factors support the poolability of the trials. This assumption was further supported by the covariate analysis, which failed to identify differences in analgesic response between studies, and by the absence of significant variation between the studies in the log dose-response relationships, as measured by the difference between mean TOTPAR of the low and high doses.

The use of covariate analysis to evaluate summary scores of analgesic response can provide substantive information about noncontrolled factors that may influence outcome in controlled trials.[13-16] Covariate-adjusted analyses have been used previously to evaluate relative treatment efficacy among subsets of patients that differ in the distribution of significant covariates. The magnitude of outcome adjustment required for any covariate depends on both the degree of disparity between the treatment groups and the strength of correlation between the covariate and the outcome variable. For example, a covariate analysis applied by Wallenstein et al in a relative potency study comparing hydromorphone and heroin demonstrated the influence of the time since last opioid dose and prior opioid intake on the analgesic response to the study drug, and allowed valid interpretation of the data.[15]

The classification of cases according to inferred pain mechanism is the most problematic element of the study. There continues to be disagreement about the definition and characteristics of neuropathic pain.[17,18] For example, there is ongoing debate as to whether pain caused by tumor compression of a nerve is nociceptive, mediated by putative nociceptive nervi nervorum, or neuropathic.[18] The definition applied in this study was inclusive, encompassing the heterogeneous pathophysiology of neuropathic pain.[1] Although the use of diagnostic criteria for the classification of pain mechanism by chart review has not been previously validated, the validity of the approach is supported by the concordance between the two independent assessors, the use of a confidence grade, and the pattern of the findings. The observations that a probable or possible nociceptive-only diagnosis had a response that tended toward that observed with neuropathic pain whereas probable or possible neuropathic-only pain yielded a response that tended toward that observed with nociceptive pain both support the validity of these confidence

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Concern about the role of a placebo response in the neuropathic group is mitigated by the use of a graded-dose double-blind technique in all the studies and the observation of a significant dose-response relationship among the patients with neuropathic pain. This dose effect, which occurred in most subgroups, would not be expected if analgesic response were due only to a placebo response. Together, covariate analyses suggest that the analgesic responsiveness observed in these studies was influenced by a variety of patient and pain factors, among which was the underlying mechanism.

The results of the analysis suggest that (1) neuropathic pains do respond to opioids but the response is generally less than that of nociceptive pain, (2) there is great variability in the magnitude of opioid response even among patients with pains of similar mechanism, and (3) there is considerable overlap between the responses of nociceptive and neuropathic pains. The finding of opioid response among neuropathic pains replicates several previous clinical studies. A placebo-controlled trial involving 19 adults with postherpetic neuralgia demonstrated analgesic effects from morphine that were significantly correlated to morphine blood levels.[19] Studies that stratified patients according to inferred pathophysiology and used patient-controlled analgesia to judge opioid response found that neuropathic pain can respond to short-term opioid treatment but is generally less responsive than nociceptive pain; in the individual patient, knowledge of the pain mechanism alone was not strongly predictive of likelihood of analgesic response to opioid therapy.[20,21]

The present analysis supports the clinical view that a trial of opioid therapy in patients with pain of sufficient severity should not be withheld or limited solely on the basis of inferred pathophysiology. Although the identification of specific patient and pain characteristics may suggest the likelihood of response, responsiveness cannot be reliably predicted in the individual patient. Given the variability of response, all opioid trials in the clinical setting should include dose titration until adequate analgesia occurs or intolerable adverse effects supervene. Although neuropathic pains may be less likely to respond in such trials, this approach will identify those responders who can gain substantial clinical benefit from opioid therapy.

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Vol. 14 No. 2 August 1997 Journal of Pain and Symptom Management 99

Review Article

Neuropathic Pain in Cancer Patients: Mechanisms, Syndromes, and Clinical Controversies

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Introduction

Pain is a complex and disturbing symptom for cancer patients and their caregivers. It has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] "Nociceptive" pain results from the stimulation of peripheral nociceptors in somatic and visceral tissues by noxious stimuli (stimuli that could be damaging to normal tissues). However, pain may also arise from disturbance of function or pathologic change in the peripheral or central nervous systems. This type of pain has been termed "neuropathic" pain. The high prevalence of painful neurological conditions in the cancer population[2,3] and the relative resistance of neuropathic pain to symptom control interventions compel the clinician to understand the assessment, diagnosis, and treatment of neuropathic pain syndromes.

Definitions

Neuropathic pain has been described as a "non-nociceptive" pain or "deafferentation pain."[4] The latter term suggests the abnormal production of impulses by neural tissue that has been divorced from afferent input. The location from which impulses arise could be within the peripheral nervous system or the central nervous system.

Nociceptive mechanisms also may be involved in the production of neuropathic pain (Figure 1). These nonciceptive mechanisms may be involved when noxious stimuli produce afferent impulses in nervi nervorum, small nerve fibers that innervate peripheral nerve and signal damage to the nerve structure.[5–7] Thus, a teleological approach could identify three categories subsumed by the term neuropathic pain: nociceptive neuropathic pain, non-nociceptive pathologic activation of peripheral generators, and non-nociceptive pathologic activation of central generators.

Causes of neuropathic pain in the cancer patient include compression or infiltration of nerves by tumor, nerve trauma secondary to diagnostic or surgical procedures, and nervous system injury (including spinal cord) following treatments, such as chemotherapy or radiation. Regardless of the category or cause, neuropathic pain may be clinically defined by several distinguishing characteristics, including abnormalities in pain quality, pain distribution consistent with neural damage, and evidence of corresponding neural injury or disease.[8]

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Accepted for publication: October 14, 1996.

Published by Elsevier, New York, New York

0885-3924/97/$17.00
PII S0885-3924(97)00009-2

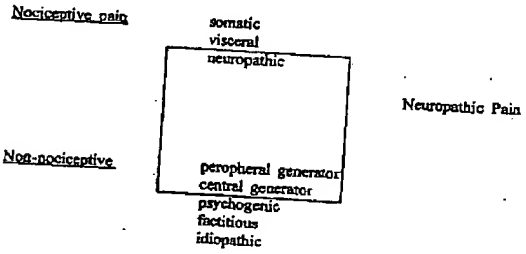

Fig. 1. Nociceptive and non-nociceptive mechanisms involved in neuropathic pain.

Abnormalities in pain quality are generally defined by the term *dysesthesia, "an unpleasant abnormal sensation, whether spontaneous or evoked."*[1]. Several forms of dysesthesia have been linked with the clinical description of neuropathic pain. These include allodynia, hyperalgesia, and hyperpathia.[1] All share an abnormal, unpleasant response to normal cutaneous stimuli. Allodynia is pain evoked by a stimulus that does not normally provoke pain. For example, allodynia may be produced by cutaneous application of stimuli normally producing the sensations of pressure or temperature. Hyperalgesia refers to a disproportionately severe pain sensation in response to a noxious stimulus, that is, an increased response to a stimulus that is normally painful. Hyperpathia is defined as a painful syndrome characterized by an exaggerated reaction to a stimulus, especially a repeated stimulus. A hyperpathic response usually occurs in an area that has an increased threshold, that is, an area that is relatively anaesthetic. The often abnormally explosive pain response can occur after a normally pain-producing stimulus or a stimulus that normally produces another sensation. Other unique characteristics associated with hyperpathia include delay, radiation, after-sensation, and faulty identification and localization of the stimulus. The broad definition of dysthesia also includes spontaneous abnormal sensations described as tingling, prickling, electric, burning, and lancinating.

Mechanisms

Much has been learned in the past decade regarding pathophysiologic mechanisms underlying neuropathic pain. These have been extensively outlined elsewhere.[9–11] The discussion herein will focus on the major categories of mechanisms for which experimental and clinical evidence currently exists. These putative categories of mechanisms are of interest in understanding the more common clinical expressions of neuropathic pain.

Neuropathic pain is not a discrete pathophysiologic entity. Portenoy[10] has described a clinical division of neuropathic pain mechanisms according to the inferred location (peripheral or central) of the pain "generator." Three major categories include deafferentation pain, sympathetically maintained pain, and peripheral neuropathic pain, each of which has many distinct postulated mechanisms. This division has intrinsic appeal in that central and peripheral nervous system pathology results clinically in different types and patterns of dysesthesia and different responses to therapeutic interventions. For instance, continuous spontaneous pain is frequently described by patients with central pain, causalgia, reflex sympathetic dystrophy, or painful phantoms,[9] all of which fall under the category of deafferentation pain.

Altered responses (in magnitude or quality) have been demonstrated after specific stimulation experiments using normal nerves. These may underlie the pains experienced spontaneously in association with evidence of nerve injury. For instance, "wind-up" has been demonstrated in the laboratory as a normal electrophysiologic effect whereby repeated stimulation of undamaged C-fiber nociceptors causes an increased response in spinal dorsal horn neurons. Price et al. has described a type of wind-up effect that follows activation of A beta low-threshold mechanoreceptors and produces burning pain in patients with reflex sympathetic dystrophy.[12]

The typical quality of pain in response to noxious stimulation of the skin and muscles can be shown to relate to selective activation of specific nociceptor fibers.[13,14] Thus, pricking and burning pains are part of normal experience after being stabbed by a pin or touching a hot surface, respectively. Neuropathic pain sensation is described as "electric or shock-like" may be likened to the electrical pains produced in normal subjects by transcutaneous stimulation of somatosensory nerves or direct stimulation of exposed nerves; in the latter cases, pain quality is dependent on the frequency and intensity of stimulation.[13,15] Pro-

gressive increases in frequency and intensity can produce sensations ranging from non-painful taps and tingling or buzzing sensations to sharp stabbing and burning pains. This progression correlates with a gradual recruitment of different types of nociceptive nerve fibers.

Other mechanisms have been demonstrated exclusively in nerve injury models. Damage to peripheral nerves may induce sensitization of nociceptors to cutaneous stimulation[16,17] and epinephrine[18–20] and may also induce altered processing in central neurons of the spinal cord. This altered processing is characterized by changes in both excitability and extent of receptive field.[21–23] Spontaneous discharges in neuromas formed after nerve transection may play a role in shooting pains described after nerve damage.[21] In addition, several mechanisms of neuropathic pain demonstrated in rat models support the existence of inflammatory or nociceptive nerve pain.[24–26]

Clinical Assessment

Several principles apply when evaluating pain in a cancer patient. First, pain should be considered an expected part of the clinical course of the disease. Because pain is such a frequent symptom, questions regarding the presence and status of painful symptoms should be a regular part of every encounter with a health-care worker. Second, the validity of a patient's pain experience should be affirmed and his or her pain intensity ratings should be used to guide investigation and treatments. Physicians and nurses often estimate their patients' pain experience inaccurately.[27] Third, multiple pain complaints are common among cancer patients, and somatic and neuropathic pains frequently coexist.[28] A thorough evaluation therefore requires an assessment of the characteristics of each pain or pain component.[29]

A complete history of pain should encompass past medical history and a chronology of the cancer.[8] This may include presentation at diagnosis, cancer treatments, complications of treatment, and circumstances of relapses. Also important is a history of pain response to previous therapies including surgery, chemotherapy, radiation therapy, anesthetic procedures, physical measures, and analgesic or non-analgesic medications. Other symptoms that occur during the time course of the pain must also be elicited; these may indicate patterns of tissue damage or point to cancer recurrence as the etiology of new pain. The history should elicit a rating of pain intensity. Pain intensity is often rated on a verbal rating scale or a numeric scale between zero (no pain) and ten (the worst pain imaginable). Other tools including visual analogue scales have been devised to assess this parameter.[29,30] Quantity of pain on average, at maximum intensity and at minimum intensity, and changes of pain intensity with various maneuvers and with recent use of medication are all helpful descriptors to characterize the pain experience. Once a baseline level of pain has been identified, the continued use of a validated pain assessment technique over time will provide a reliable measure of a patient's response to therapy.

A multidimensional pain description can be elicited through use of the McGill Pain Questionnaire (MPQ) which is often used as a validated research tool. The MPQ contains 78 adjectives that cluster in 20 categories and assess the sensory, affective and evaluative components of pain. Its limitations include unreliable summary measurement of pain over a defined period of time, and difficulty in fitting cancer pains into the specified pain patterns of the MPQ.[31]

Pain History and Neuropathic Pain

Descriptions of pain quality are useful to characterize neuropathic pain. Neuropathic pain is often described as a dysesthesia: lancinating, burning, pressure or vice-like, electric, shock-like, pricking, and tingling.[9,32,33] There may be spontaneous paroxysmal pains in addition to underlying constant pains.[9] Allodynia is often spontaneously reported as severe pain caused by contact with bedclothes or undergarments.[9] Abnormal responses to pressure, warmth, cold, and light touch should be queried and patients should be asked whether a stimulus results in an unpleasant sensation, abnormal intensity, delay, radiation, localization, or after-sensation.

The location of the pain should be described, with particular attention to patterns consistent with nerve damage.[8] Thus a pain may be described in the distribution of a peripheral nerve, as dermatomal or represent-

ing damage to a nerve root (radicular), in the distribution of multiple nerve roots (polyradicular or plexus), as a larger region such as that innervated by a damaged central pathway, or as a symmetrical pain in the extremities, for example, painful peripheral neuropathy or myelopathy or of higher origin.

In contrast, somatic and visceral nociceptive pains are usually described in different qualitative terms. Somatic pains have been described as well localized, with sharp, aching, throbbing, or pressure-like qualities. Visceral pains are usually less well localized and may be referred to characteristic cutaneous sites. Qualitative descriptors may depend on the nature of visceral involvement. Thus, obstruction of a hollow viscus results in crampy gnawing pain, whereas sharp throbbing pain is reported in cases of organ capsule involvement.[8]

The ability of cancer pain patients to provide qualitative descriptors spontaneously may be quite limited, presumably due in part to limited vocabulary to articulate the experience and to the unfamiliar quality of some neuropathic pains.[34] Thus, the use of pain descriptor lists such as those contained in the MPQ may assist qualitative evaluation.

Last, the history should evaluate for other neurologic symptoms. These may be anesthesia or hypesthesia (increased threshold for sensory detection) to a variety of sensory modalities; weakness; or sympathetic nervous system involvement (including vasomotor changes and dystrophic changes).

Examination

The physical examination in patients with neuropathic pain must include a detailed neurologic examination. A systematic sensory examination should concentrate on areas related to the location of pain and should include testing of all cutaneous modalities and even repeated stimuli (to elicit hyperpathia). Observation for sympathetic changes will also be important. The physical examination should include provocative maneuvers to try to elicit the pain; a positive provocative maneuver can have diagnostic significance.

Diagnostic Investigations and Neuropathic Pain

Diagnostic studies should be guided by findings on history and physical examination, familiarity with common modes of spread of the patient's cancer, and knowledge of the common neuropathic pain syndromes (see below). A review of previous laboratory and imaging studies is important[8] and may, with the aid of new clinical information, provide a retrospective diagnosis. Algorithms have been determined for the investigation of some common syndromes, such as back pain in the cancer patient, and these may serve as useful guides to diagnosis.[35,36]

In evaluating cancer patients with neuropathic pain, computerized tomography (CT) or magnetic resonance imaging (MRI) can be invaluable. CT may be sufficient when defining bone and soft tissue abnormalities. MRI provides optimal visualization of epidural spinal cord compression, nerve root impingement and parenchymal brain metastases.[29] Bone scintigraphy will provide evidence of metastatic bony disease or a pattern consistent with direct bony extension, which may fit the clinical picture of adjacent nerve involvement.

In selected circumstances, tumor markers such as carcinoembryonic antigen (CEA) in colon carcinoma may support the suspicion of recurrent disease and allow an etiologic diagnosis. As in all investigative procedures, however, false-negative results can occur; clinical judgment and a high degree of clinical suspicion should dictate further evaluation or monitoring if the clinical picture is consistent with nerve compromise.[37,38]

Each laboratory and imaging study should be personally reviewed, with particular attention to areas of potential disease identified by known clinical information.[8,29] In addition, it has been wisely stressed that pain must be managed during the process of evaluation;[8] pain therapy can be tailored once the results of investigation are known.

Evaluation of a patient with possible neuropathic pain is critical to identify new treatable pathology in a cancer patient. In a review of cancer pain patients referred to the Pain Service at Memorial Sloan-Kettering Cancer Center, new previously unsuspected lesions were identified through a pain evaluation in 64% of consultations and a large proportion of these were neurologic.[2] Many of these patients were then considered for primary antineoplastic therapie.

Validity of Clinical Classification

The ability of clinicians to distinguish among neuropathic and other pain mechanisms has not been systematically studied. Studies that have evaluated the utility of verbal descriptors to distinguish among pain syndromes have yielded mixed results. For example, studies using the MPQ have had variable success in distinguishing between neuropathic and non-neuropathic pain among patients with non-malignant disease. A pain questionnaire based largely on the MPQ was not successful in differentiating four pain categories in patients with nonmalignant pain, one of which included the diagnosis of peripheral neuropathy.[39] In contrast, the MPQ has been shown to correctly classify 91% of patients as having trigeminal neuralgia versus atypical facial pain on the basis of seven descriptors.[40] A similar level of discrimination was achieved by the MPQ for patients with painful diabetic neuropathy versus patients with painful legs or feet of other etiologies.[41]

Several studies have assessed the ability of qualitative descriptors to distinguish cancer pain according to etiologic classification. Boureau et al.[33] used a French adaptation of the MPQ to compare verbal description of pain between a group of patients with neuropathic pain and a mixed group of cancer patients with chronic nonmalignant pains. Seventeen descriptors had a significant intergroup frequency difference. The words that were chosen with increased frequency in the neuropathic pain group included burning, electric shock, tingling, pricking, itching, and cold. Seven descriptors in a discriminant function analysis correctly assigned 77% of neuropathic pain patients. Validation with a second group of patients with neuropathic pain permitted diagnostic categorization in 66%.

The latter finding conflicts with another survery of cancer patients who were asked to describe their pains using their own words. No differences were found in word usage with respect to cancer pain etiology (bone, nerve, or soft tissue).[34]

Cherny et al.[28] classified patients with chronic cancer-related pain according to inferred pain mechanisms. This classification was determined by independent review of case records by two experienced pain clinicians. Pain mechanisms were labelled as having neuropathic or nociceptive components and were graded as to the degree of confidence in each inferred mechanism. The criteria for inference of a neuropathic mechanism included suggestive pain qualities (for example, associated dysesthesias or paresthesias), distribution of pain consistent with neural damage, and other evidence of corresponding neural injury or disease. Concordance between the two assessors was 72% for pains with a neuropathic component and 91% for pains with a nociceptive component. Overall agreement was 65%. Classification also revealed a substantial overlap for these two mechanisms: a neuropathic mechanism alone was the cause of pain in 10% of cases whereas the percentages for nociceptive pain alone and mixed mechanisms were 49% and 41%, respectively. Classification of pain as neuropathic in a clinical cancer staging system has been shown to predict prognosis with respect to effective analgesic treatment.[42]

In summary, results of studies assessing the ability to differentiate neuropathic from other forms of cancer pain on the basis of qualitative descriptors provided by patients or clinical assessment by physicians indicate that, although possible, discrimination is only modestly reliable and therefore variably successful. This underlines the necessity for a high index of suspicion and an awareness of the frequent coexistence of multiple pain mechanisms in any given cancer pain patient. Instruments such as the MPQ may be helpful in differentiating neuropathic pain using descriptors.

Differential Diagnosis

When evaluating a cancer patient who appears to have neuropathic pain, the clinician develops hypotheses regarding potential causes. Underlying pathology encompasses a broad spectrum of disorders, including recurrent or progressive neoplasm, direct side effects of cancer treatment, and causes related to neither the cancer nor its treatment. Certainly, any mechanism of nerve injury known to occur in non-cancer patients may also occur in cancer patients.

Cloughston et al.[5] prospectively evaluated a consecutive series of neurological problems in patients with a history of systemic cancer. In

133 patients with undiagnosed back or neck pain, 15% were found to have etiologies unrelated to metastatic disease. The most common non-metastatic cause of pain was degenerative disease of the spine. Other causes included epidural abscess, vertebral crush fracture from osteoporosis, and subcutaneous hematoma.

Other neurologic syndromes have similarly broad differential diagnoses. Lumbosacral plexopathy has been reported following embolization of bleeding rectal lesions, local hemorrhage, aortic aneurysm, and vasculitis.[43,44] Peripheral neuropathies have numerous causes including metabolic disorders, nutritional deficiencies, infections, and vasculitis.

Infection can cause intractable escalating pain. Examples been reported in patients with advanced head and neck tumors,[45] and in patients with metastatic breast cancer and post-radiation pain syndrome.[46] Cancer patients are often immunosuppressed and have disrupted tissue barriers, thereby increasing risk of infection. The diagnosis of unsuspected infection was established in 6% of cancer patients referred for evaluation by a pain consultant service; empiric antibiotics must be considered when infection is a possibility.[2]

Clinical Implications

Opioid Responsiveness

It has been traditionally held that opioid responsiveness of pain can distinguish between neuropathic and nociceptive pain.[47,48] However, most clinical trials evaluating opioid responsiveness of neuropathic and nociceptive pain syndromes have discovered relative, rather than absolute differences. This remains an area of controversy.

In one of the first systematic studies of opioid responsiveness and neuropathic pain, Arner and Meyerson[49] reported that morphine or equivalent opioids failed to produce "moderate or complete" pain relief in patients with longstanding neuropathic pain, as defined by mononeuropathy, plexopathy, myelopathy, or deafferentation. In contrast, excellent pain relief was experienced by patients with chronic visceral pain, including pancreatitis. It was thus suggested that an "opioid test" could be used as an analytical tool to distinguish between these types of pain.

An early retrospective survey of pain relief in a large group of cancer patients revealed that pain characteristics were associated with differences in the analgesic response to intramuscular morphine.[50] Patients with "dull" pain obtained pain relief at one-half the dose of morphine compared with patients with "sharp" pain. However, two patients with "radiating and shooting" pain obtained high scores of pain relief at increasing doses of morphine.

Kupers et al.[51] reported a differential effect of opioids on neuropathic versus idiopathic pain in a double-blind placebo-controlled trial, with idiopathic pain responding more readily than neuropathic pain. Although overall pain scores in the neuropathic pain group were reduced in a dose-dependent fashion, opioid had no effect specifically on pain sensory ratings. The authors concluded that an apparent therapeutic effect of morphine in neuropathic pain may be mediated through decrease in associated affect rather than through modification of afferent signals.

Other evidence suggests that opioids do reduce neuropathic pain. Rowbothan et al.[52] demonstrated a decrease in pain intensity and associated allodynia in patients with well established postherpetic neuralgia after intravenous infusion of morphine. Other case studies and case series have reported successful control of non-malignant neuropathic pain with opioids.[53–55] Opioid dose escalation studies have demonstrated moderate pain relief in patients with primarily cancer-related neuropathic pain syndromes.[56]

Jadad et al.[57] utilized two dose levels of patient-controlled analgesic (PCA) in a double-blind randomized crossover design for patients with varying types of chronic pain. Neuropathic pain did respond to opioid, although with a less consistent magnitude of effect than nociceptive pains. The two patients with cancer-related neuropathic pain both showed positive responses. Notably in this study, the opioid effect was considered independent of affect, as there was no change in mood in the absence of a change in pain intensity.

Cherny et al.[28] evaluated opioid responsiveness as measured by total pain relief score for patients whose cancer pain syndromes were classified as neuropathic or nociceptive. The pain relief provided by single graded doses of

Table 1
Adjuvant Analgesics

Tricyclic antidepressants	Amitriptyline
	Desipramine
Anticonvulsants	Carbamazepine
Local anesthetics	Lidocaine
	Mexiletine
Neuroleptics	Haloperidol
Other	Capsaicin (topical)
	Clonidine

an opioid was significantly lower for the neuropathic pain group than for the nociceptive pain group. These results appear to support the traditional view that neuropathic pain responds less well to opioids than nociceptive pain. However, the study revealed "a great overlap in responsiveness of pains mediated by neuropathic, nociceptive and mixed pain mechanisms." In addition, there was a significant dose-response relationship among the patients with neuropathic pain. This would suggest that there is a continuum of opioid responsiveness for pains described as neuropathic.

One reason for the apparently disparate responses of neuropathic pains to opioid drugs among published reports may be a failure to differentiate the so-called nociceptive neuropathic pain from deafferentation pain.[58] Pain due to peripheral nerve involvement by tumor may show more opioid sensitivity, particularly if a deafferentation component is absent or less marked than the nociceptive component.[59]

Evaluation of response of neuropathic pain to opioids requires well-designed randomized clinical trials, which must take into consideration the heterogeneous population of patients with neuropathic pain and differentiate patients by subgroup according to etiological and pathological mechanisms.[60] The bulk of currently available evidence supports a continuum of opioid responsiveness for patients with neuropathic cancer pain.

Adjuvant and NonOpioid Analgesics

Nonopioid analgesics [such as acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDS)] and adjuvant analgesics have been widely used—and misused—in the treatment of cancer-related neuropathic pain syndromes (Table 1). Clinical experience has affirmed the utility of combining an NSAID or acetaminophen with an opioid.[61] The nonopioid may yield an additive, and therefore opioid-sparing, effect. Standard cancer pain algorithms include the early institution of opioid-nonopioid combinations, and these principles also hold for neuropathic pain.[10]

The use of adjuvant analgesics in the treatment of neuropathic pain is now widely accepted.[62] Adjuvant analgesics are medications with other primary indications that are analgesic in some painful conditions. The most accepted of these agents in the treatment of neuropathic pain are the tricyclic antidepressants and anticonvulsants.[63] Antidepressants, particularly the tricyclic drugs such as amitriptyline and desipramine, have demonstrated effectiveness in postherpetic neuralgia and mixed neuropathic pains of nonmalignant etiology.[64–70] Neuropathic cancer pains also appear to respond to these tricyclic compounds.[63,69,70] The anticonvulsant drugs are most useful in the treatment of lancinating pains of paroxysmal onset.[71,72] For example, carbamazepine has been shown to be effective in the treatment of neuropathic pain.[63,73,74]

Other adjuvant analgesics may be useful in the treatment of neuropathic pains, but are generally considered second-line agents for pains refractory to tricyclic antidepressants and anticonvulsants. For example, baclofen appears to be effective in the treatment of trigeminal neuralgia,[75] but has not been extensively studied in other types of neuropathic cancer pain. Oral local anesthetics such as tocainide, mexiletine, and flecainide may be used in the treatment of a variety of lancinating or constant dysesthetic pains.[76–79] Intravenous or subcutaneous lidocaine has demonstrated only variable effectiveness in neuropathic cancer pain,[80–82] and the apparent disparity in analgesic outcome between cancer-related and non–cancer-related neuropathic pain is not understood and remains an area of clinical controversy. It is possible that the concurrent pathophysiological processes contributing to the development of cancer-related neuropathic pain—both nociceptive and non-nociceptive—may account for the variable and apparently unpredictable analgesic response to systemic local anesthetics in this population. Neuroleptics,[79] topical capsaicin,[83,84] and oral or transdermal clonidine[85,86]

have also been used for neuropathic pain, and corticosteroids,[87] phenoxybenzamine, prazosin, and nifedipine[79] have been administered to those with sympathetically maintained pain.

Sympathetic Blockade

If a sympathetically maintained pain is suspected on the basis of clinical characteristics, sympathetic blockade should be considered for diagnostic and, perhaps, therapeutic purposes.[88] The possibility of sympathetically maintained pain should be entertained whenever neuropathic pain is accompanied by local signs of autonomic dysregulation (for example, vasomotor changes, sweating disturbances, or local swelling) or trophic changes. It is important in patients who have painful brachial plexopathy associated with arm swelling and erythema to consider the possibility of sympathetically maintained pain and not to simply assume an associated obstruction of venous outflow or lymphatics.

Epidural Injections

Epidural opioid administration is occasionally helpful in patients with neuropathic cancer pain who have not responded to aggressive systemic opioid.[47,89–91] Epidural administration of local anesthetics, particularly bupivacaine, also has shown encouraging results in cancer patients with neuropathic pain, especially those failing opioid treatment.[90–94] Recently, epidural clonidine has been shown to produce successful analgesia in intractable cancer pain, particularly in neuropathic pain.[95]

Response to Neurosurgical Interventions

Clinical experience suggests that the likelihood of a poor response following neurolytic procedures is greater in neuropathic than nociceptive pain.[96–98] A favorable response to local anesthetic block does predict the efficacy of neurolysis.

It is possible that neuropathic pains with different mechanisms have differential responses to neurolytic procedures. A deafferentation pain may be worsened, whereas a peripheral neuropathic pain with no central mechanism involved may be ameliorated. For example, peripheral blocks have shown clinical efficacy in treatment of brachial plexus neuropathies.[99,100] Because of the concern about worsening pain, nondestructive approaches are often considered. For example, neurostimulation procedures may be helpful in neuropathic pain.[101,102]

Neuropathic Pain Syndromes in Cancer Patients

Cancer pain syndromes have been well described in many recent reviews.[8,29,103] The discussion herein will focus on those syndromes that commonly present with a major element of neuropathic pain.

Neuropathic Pain Secondary to Cancer-Related Pathology in Cranial Nerves

Painful cranial neuralgias may occur secondary to base of skull metastases, leptomeningeal metastases, or head and neck cancers.[104] Base of skull metastases are characterized by several well-described syndromes[105] and are often associated with primary tumors of the breast, lung, and prostate, as well as others. Constant localized aching pain from bone destruction and neurologic deficits from progressive cranial nerve palsies are cardinal manifestations. In general, the evaluation for neuropathic pain associated with cranial nerve dysfunction should include imaging of the head with CT and MRI, and sometimes cerebrospinal fluid analysis with cytology.

The middle cranial fossa syndrome presents with facial numbness, paresthesias or dysesthetic neuropathic pain in the distribution of the second or third divisions of the trigeminal nerve. Associated motor deficits include weakness in the masseter or temporalis muscles or abducens palsy.

The jugular foramen syndrome may present as glossopharyngeal neuralgia.[105] This pain is distributed over the ear or mastoid region and may radiate to the neck or shoulder. Associated deficits include a Horner's syndrome and paresis of the palate, vocal cords, sternocleidomastoid muscle, or trapezius muscle. This syndrome has also been described as the result of leptomeningeal metastases[106] and local extension of head and neck malignancies.[107] It can be associated with syncope.[108]

A syndrome which clinically mimics classical trigeminal neuralgia has been reported secondary to tumors in the middle or posterior fossa[109–112] or from leptomeningeal

metastases.[113] This association between trigeminal neuralgia and tumor is not uncommon, and cancer patients with a new onset of trigeminal neuralgia should have careful imaging of the base of skull.[110,111]

Postherpetic Neuralgia

Although not caused directly by tumor, postherpetic neuralgia is more frequently seen in association with malignancy.[1,14] Acute herpetic infection has also been shown to occur in specific sites related to the primary tumor.[115,116] A suggested definition for postherpetic neuralgia is a persistence of pain in the region of the original herpetic infection for a period of at least 2 months after the disappearance of the skin eruption.[114] The pain assumes a dermatomal distribution.

Tumor-Related Mononeuropathy

The most commonly described tumor-related painful mononeuropathy is intercostal nerve injury secondary to rib metastases with local extension.[29] Tumor invasion of the sciatic notch has also been reported and presents with symptoms suggestive of sciatica.[8]

Other Neuralgias

Sharp, shooting neuropathic pain can develop along the distribution of virtually any sensory nerve, and would appear to respond to the same analgesic interventions as the better studied cranial neuralgias.[117] Invasive cancer should be suspected and evaluated with appropriate imaging studies. Radiation damage or systemic neuropathy can cause similar pains.

Radiculopathy

A radiculopathy may be characterized by dermatomal pain in the territory innervated by the dorsal (sensory) spinal roots. Cancer-related radiculopathy may present on either or both sides of the midline, and tends to be unilateral in the cervical and lumbosacral regions and bilateral in the thorax.[118] In cancer patients, it is most commonly caused by an epidural tumor mass or leptomeningeal metastases. The pain, which often has dysesthetic qualities, is exacerbated by cough, sneeze, recumbency, and strain.

The implications of painful radiculopathy for urgent diagnosis of associated spinal cord compression and algorhithms for clinical diagnosis have been well described elsewhere.[58,119–121] MRI is considered the best imaging modality,[122] although there have been no systematic trials comparing MRI with CT myelography. Several prognostic indicators, when present in addition to radicular pain, can increase the probability of concomitant epidural cord compression. These include central back pain occurring in a rapid crescendo pattern;[118] the presence of an abnormality on plain radiograph at a level consistent with the clinical findings, especially if there is greater than 50% vertebral body collapse or pedicle erosion;[123] and positive scintigraphy at an appropriate level.[124] A careful evaluation is essential. Cancer patients with radiculopathy due to lumbar disc have been wrongly diagnosed with epidural tumor, and treated with oncologic interventions including radiation therapy or castration.[125]

Radiculopathy may also develop secondary to leptomeningeal metastases. Clinically, leptomeningeal metastases may produce multifocal neurological signs and symptoms at a variety of levels, including cranial neuralgias. Most commonly, they produce a generalized headache with radicular pain in the low back and buttocks.[126] Lumbosacral radiculopathy may occur because gravity predisposes cancer cells to settle on the nerve roots of the cauda equina. There may be other accompanying symptoms, including change in mental status, seizures, hemiparesis or ataxic gait. Diagnosis may be made on the basis of cerebrospinal fluid (CSF) cytology, which is positive in up to 90% of cases if at least three lumbar punctures are performed.[127] MRI with gadolinium enhancement is the most sensitive imaging test. In a series of breast cancer patients with leptomeningeal metastases treated with radiation, corticosteroids, and intraventricular or intrathecal chemotherapy, median survival was 7 months.[128] The survival for untreated patients, or for patients with treatment refractory neoplasms, such as squamous cell carcinoma, is usually 4–6 weeks.

Cervical Plexopathy

Infiltration of the cervical plexus by tumor can produce several pain syndromes, depending on the pattern of nerve involvement.[129] Common clinical settings include local exten-

sion of a head and neck tumor or cervical lymph node metastases. Pain can occur in the preauricular area (greater auricular nerve), postauricular area (lesser and greater occipital nerves), anterior neck (transverse cutaneous and supraclavicular nerves), and other areas of the head and neck. Associated findings include ipsilateral Horner's syndrome or hemidiaphragmatic paralysis. CT or MRI evaluation may be necessary to rule out associated epidural cord compression.

Brachial Plexopathy

Neuropathic pains due to tumor infiltration of the brachial plexus most frequently occur as a result of lymph node metastases from breast carcinoma or lymphoma, or direct extension from lung carcinomas (that is, Pancoast tumor).[35] Pain occurs in 85% and often precedes neurologic deficits.[130] Lower plexus involvement is most common when tumor arises from the lung apex; pain and dysesthesias involve the elbow, medial forearm and fourth and fifth fingers (C7, C8, T1). Upper plexus involvement (C5, C6), if it occurs alone, will usually develop into a panplexopathy.[35] Associated findings can include Horner's syndrome and adjacent vertebral disease; such patients are at high risk for concurrent epidural extension.[125,127] Evaluation includes CT or MRI;[111] EMG can be useful to distinguish malignant brachial plexopathy from radiation-induced brachial plexopathy or cervical radiculopathy.[131] A Spurling's maneuver can be used to identify the spinal canal as the site of pathology.[132]

Lumbosacral Plexopathy

Direct extension of colorectal carcinoma, cervical carcinoma, sarcoma,[133] or lymphoma or breast metastases are the most frequent causes of lumbosacral plexopathy.[113] Pain is often the first symptom, and eventually appears in almost all patients. Associated weakness involves multiple myotomes, and sensory loss crosses dermotomes. Autonomic dysfunction is common in any plexus lesion and can actually precede other symptoms.[134,135]

Lumbosacral plexopathy may cause different clinical syndromes depending on the level of nerve involvement. Involvement of the upper plexus occurs in approximately one third of patients, and presents with pain in the back, lower abdomen, flank, iliac crest, anterolateral thigh, and has associated L1–L4 distribution neurological deficits.[133] Specific syndromes have been described[136] and include the L1 syndrome, pelvic sidewall syndrome, and malignant psoas syndrome.

Involvement of the lower plexus occurs in approximately one-half of patients and presents with pain in the buttocks and perineum with referral to the posterolateral leg and thigh. Examination may reveal associated L4–S1 neurological deficits, leg edema, bowel or bladder dysfunction, and surprisingly, a positive straight leg raise test.[133]

Sacral plexopathy may result either from direct extension of a bony sacral lesion or a presacral mass. Numbness of the dorsal medial foot and sole with associated weakness of knee flexion, ankle dorsiflexion, and inversion is typical of lumbosacral trunk involvement.[113] Involvement of the coccygeal plexus results in sphincter dysfunction and perineal sensory loss.

Pan plexopathy occurs in one fifth of patients and findings may be referable to anywhere in the territory of the plexus. Associated leg edema in this situation is relatively common.[134]

Paraneoplastic Peripheral Neuropathy

A subacute sensory neuronopathy or ganglionopathy can present with dysesthesias, paresthesias and sensory loss in the extremities.[137] This represents an inflammatory process involving dorsal root ganglia and may be caused by an antineuronal IgG antibody. The course is usually independent of the primary tumor, which is commonly small cell carcinoma of the lung.[138] Sensorimotor peripheral neuropathies presenting with glove and stocking distribution may also be associated with malignancy, with production of antibodies against peripheral nerves.[139]

Central Pain Syndromes Caused By Cancer

Central pain syndromes are relatively infrequent in the cancer population.[140,141] In a consecutive series of 72 patients with central pain due to chronic spinal cord lesions, none were related to malignant tumor, although six were related to benign tumors.[140] While epidural spinal cord compression is almost always

painful, it is not characterized by central pain as the predominant symptom; pain is usually caused by nociceptive input from progressive bony destruction by metastases, with or without concurrent radicular pain from nerve root compression.[141] Radiation myelopathy may be considered a central pain syndrome.

In a series of 50 patients with central pain caused by brain lesions, none were caused by neoplastic lesions.[140] The low likelihood of a destructive central nervous system neoplasm to cause central pain likely relates to the shortened life span of patients with malignant lesions. Central pain often develops long after the causative central nervous system insult.[119]

Neuropathic Pain Secondary to Therapeutic Interventions

Neuropathic Pain Related to Analgesic Interventions

High-dose intrathecal and epidural injections of opioids may result in neuropathic pains. These may include perineal, buttock or lower extremity pain with concomitant hyperalgesia. Associated neurologic symptoms include segmental myoclonus, piloerection, and priapism.[142,143] Extremely high-dose parenteral opioid infusions can cause generalized myoclonus and convulsions. Treatment involves rotation to a different opioid[144] and the institution of a benzodiazepine such as midazolam by infusion.

Epidural Injection Pain

Anesthetic epidural injections may cause neuropathic pains in approximately 20% of patients.[145] Typically this consists of back, pelvic or lower extremity pain, and is self-limited. These symptoms are thought to be caused by compression of an adjacent nerve root.

Post-Surgical Neuropathic Pain

Post-mastectomy. Chronic neuropathic pain after mastectomy occurs primarily in patients whose surgery included axillary dissection. The incidence of post-mastectomy pain in this setting may be as high as 20%. The pain consists of a constricting or burning discomfort localized to the anterior chest wall, axilla, and medial arm.[146,147] This syndrome follows either a subacute or chronic course. The etiology appears to be surgical damage to the intercostobrachial nerve.[146] Usually, the pain develops shortly after surgery; later onset should prompt a search for other causes such as recurrent chest wall disease. The clinician should also carefully evaluate for the presence of concomitant frozen shoulder, or bone metastases.

Neck dissection Radical neck dissection for head and neck cancers can result in a syndrome characterized by pain over the ipsilateral face and neck with associated paresthesias. This usually occurs weeks to months after surgery and is secondary to injury to the cervical plexus.[148] It is important to differentiate this from a chronic pain that develops after neck dissection and is presumably due to an imbalance in the function of neck muscles and can be complicated by development of a thoracic outlet syndrome. Recurrent cancer must also be considered when pain occurs after neck dissection.

Thoracotomy. Shortly following thoracotomy, a neuropathic pain may develop that is usually in the distribution of one or several intercostal nerves. This pain usually remains stable after onset and gradually decreases over a period over months or years.[149] Pain that increases with time or first appears more than 3 months after surgery is usually due to recurrent tumor, and should prompt an investigation.

Phantom Pains

Phantom pain is perceived to arise from a body part which has been surgically removed, and is perceived as if the part were still anatomically present. The best studied of these syndromes is phantom limb pain. The pain may be continuous or paroxysmal and is associated with dysesthesias. The phantom limb may also assume abnormal postures and may gradually telescope. The incidence of phantom limb pain is greater if pain was present in the limb prior to amputation.[150]

Phantom breast pain has been reported in 15%–50% of patients following mastectomy.[151] Phantom anus pain occurs in 15% of patients after surgery for rectal carcinoma.[152] A phantom bladder pain has also been reported.[153] There is preliminary evidence that the incidence of phantom pain may be reduced with the establishment of preoperative analgesia via

epidural catheter.[154] Treatment of phantom pain often includes adjuvant analgesics, such as carbamazepine, with or without opioids and anti-inflammatory drugs or acetaminophen. The reappearance or worsening of phantom pain a long time following amputation can herald the appearance of tumor recurrence.[155]

Localized stump pain occurs after limb amputation at the site of the surgical scar. It is characterized by burning or lancinating pain with associated dysesthesias, and develops months to years after amputation. Stump pain usually indicates the existence of a neuroma in the scar after nerve resection;[156] a Tinel's sign over the stump confirms this diagnosis. Non-neuropathic stump pain has a variety of causes, including stump ischemia, infection, bone spur, or a poorly fitting prosthesis.[157] The clinician must carefully distinguish phantom pain, non-painful phantom sensations, neuropathic stump pain, and non-neuropathic stump pain.

Radiation Myelopathy, Plexopathy, and Neuropathy

Subacute radiation myelopathy may occur after radiotherapy of extraspinal tumors; it is most commonly seen in the cervical cord after treatment for head and neck cancers[158] and following treatment for Hodgkins disease.[159] The syndrome is described as shock-like pains in the neck precipitated by neck flexion (Lhermitte's sign), which may radiate down the spine and into the extremities. The syndrome begins one to several months after treatment and resolves after a few months to a year. It may be produced by dose levels well below those causing chronic radiation myelopathy.[159,160] Pathogenesis may be related to a transient demyelination.[161]

A bimodal distribution of chronic myelopathy, a late complication of spinal cord irradiation, suggests the existence of different underlying mechanisms.[162] The early delayed type occurs 6–8 months after treatment and is related to demyelination and necrosis of the white matter. The late delayed type typically begins 1–4 years afterward and relates more to vascular damage.[161] Pain typically precedes development of neurological signs and is localized to dermatomes at or below the level of the damage.[158] Spinal cord signs consistent with a partial transverse myelopathy eventually develop.[163] Some patients develop a Brown-Sequard syndrome with unilateral weakness, pyramidal tract signs, and contralateral sensory deficits. No specific treatment has been developed but corticosteroids are often tried to reduce edema.[160]

Neuropathic syndromes associated with chest wall/axillary radiotherapy include brachial plexopathy, malignant peripheral nerve tumors, nerve entrapment in a lymphedematous shoulder, and ischemia.[8] Both early and late onset brachial plexopathy have been described. Clinically, the plexopathy is characterized by mixed sensory and motor deficits with or without pain. The early onset type has a latency of 3–14 months and occurs in 1.4% 20% of irradiated breast cancer patients.[164,165] It is usually self limited.

The late-onset type can develop 1–20 years after treatment. It is less commonly associated with pain and predominantly involves the upper plexus.[35] A higher incidence was previously reported when large fraction doses (3Gy) were used.[166] The likelihood of this lesion is now less than 1% when 2Gy fractions are used to deliver a total dose of 50Gy;[160] the incidence is approximately 5% after total doses approaching 60Gy.

Paresthesias, distal weakness progressing proximally, and rarely pain in the lower extremities have been reported to occur 2–3 months after irradiation of the sacral plexus.[67] This syndrome may relate to reversible demyelination. This is a rare complication and may occur more frequently in patients following intracavitary radium implants for carcinoma of the cervix.[168] The symptoms and signs may be bilateral.[169] Recently, acute neuralgic amyotrophy of abrupt onset has been reported in four patients with onset days to weeks following radiation treatment for Hodgkin's disease.[170]

Peripheral Neuropathy Due to Chemotherapy

Various chemotherapeutic agents can cause painful peripheral neuropathy. The syndrome is characterized by painful dysesthesias in the hands and feet (glove and stocking distribution), with associated sensory, motor, and autonomic deficits. Depression of deep tendon reflexes is the most common manifestation. The chemotherapeutic agents commonly

implicated include the vinca alkaloids, especially vincristine,[171,172] and cisplatinum.[173] More recently, peripheral neuropathy has been reported secondary to treatment with paclitaxel[174] and, rarely, cytarabine.[175] Withdrawal of the offending agent may result in resolution of the neuropathy over weeks to months, although persistent neuropathies may develop after withdrawal of cisplatinum.[176]

Corticosteroid-Induced Perineal Discomfort

Large doses of parenteral dexamethasone have been followed by a transient burning sensation in the perineum.[177] This may be prevented by slow infusion.

Intrathecal Methotrexate Meningeal Syndrome

An acute meningitic syndrome manifested as headache, nuchal rigidity, fever, vomiting, and irritability occurs in 5%–50% of patients treated with intrathecal methotrexate.[178] Symptoms begin hours after the treatment and may persist for several days.

Summary

The identification of a neuropathic pain syndrome in a cancer patient requires a focused clinical evaluation based on knowledge of common neuropathic pain syndromes. If a tumor is directly involved in the etiology of the pain, oncologic treatment is an initial consideration and may include surgery, radiation, or chemotherapy.[179] There is no single accepted algorithm for the analgesic treatment of neuropathic pain and a systematic approach utilizing therapeutic trials of specific agents at gradually increasing doses is warranted. A trial of opioids, perhaps in combination with an NSAID, is warranted. If the pain is relatively unresponsive to an opioid, a trial with an adjuvant analgesic is reasonable. For example, a tricyclic antidepressant might be selected early for patients with continuous dysesthesia, and early treatment with an anticonvulsant might be used if the pain is predominantly lancinating or paroxysmal. Other adjuvant analgesics can be selected if there is insufficient response to these agents.

A trial of sympathetic blockade, pharmacologic, anesthetic or surgical, should be considered in patients with evidence of causalgia or reflex sympathetic dystrophy. Physiatric modalities such as massage, heat, or cold; counterstimulation or transcutaneous electrical nerve stimulation (TENS), and orthopedic interventions, such as braces and splints may be useful. Epidural injections or neurostimulation of the spinal cord or brain can be considered in selected cases where appropriate expertise is available.

Treatment of neuropathic pain remains a challenge for both clinicians and patients. The complexity of syndromes and underlying etiologic mechanisms warrants further clinical trials to determine the best treatment modalities for individual pain syndromes.

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Seminars in
Arthritis and Rheumatism

VOL 27, NO 1 AUGUST 1997

Chronic Pain States: Pathophysiology and Medical Therapy

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Objective: The pathophysiology and management of chronic pain are reviewed in this two-part article, with an emphasis on pharmacological therapies and surgical interventions.

Data Sources: A thorough literature review of published articles available in Medline from 1966 to 1996 on the topic of pain management, including diagnosis, pathophysiology, interventions, and treatment.

Conclusions: Despite the development of new instruments and treatments to assess and manage pain, chronic pain is often poorly understood and inadequately addressed. Caregivers often lack sufficient skills to intervene promptly and effectively. Traditionally, drug therapy has relied on the nonsteroidal antiinflammatory drugs (NSAIDs) and opioid analgesics for chronic nociceptive pain. A newer analgesic choice for moderate to moderately severe pain is tramadol, a centrally acting agent with at least two complementary mechanisms of action and minimal gastrointestinal or renal toxicity. Adjuvant agents, including tricyclic antidepressants (TCAs), anticonvulsants, and local anesthetics, also help manage chronic neuropathic pain. Although significant advances in the understanding of chronic pain and its pathophysiological mechanisms and newer techniques (noninvasive and invasive) for chronic pain management have become available, reduced patient morbidity and improved quality of life may only be realized with an improved understanding of available resources.

Semin Arthritis Rheum 27:1-16. Copyright © 1997 by W.B. Saunders Company

INDEX WORDS: Chronic pain; analgesics; adjuvant therapy; invasive procedures.

PAIN IS A normal physiological response to potentially noxious stimuli and may be viewed as an efficient signal mechanism against harmful stimuli in the environment. However, pain may become chronic and undesirable, creating and contributing to overall patient morbidity. Results from studies of patients with cancer-related pain indicate that the prevalence of pain is 50% to 70% in early stages of cancer and 60% to 90% in later stages. It is estimated that more than 1 million Americans experience cancer-related pain annually, and most do not receive effective pain relief (1). Additionally, many patients with acquired immunodeficiency syndrome (AIDS) suffer from

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0049-0172/97/2701-0001$5.00/0

pain related to progress of the disease. The cause of this pain is varied and includes somatic, neuropathic, and idiopathic sources (2). Pain is second to fever as the most common reason for hospitalization in AIDS patients, and there is a direct correlation between the presence of pain and length of hospital stay (3).

The elderly population is at an increased risk for experiencing chronic pain, with the prevalence of pain doubling after 60 years of age. Several studies estimate that 25% to 50% of community-dwelling elderly people suffer from important pain problems (4). Moreover, in nursing home patients, the prevalence of pain-related problems is estimated to be greater than 70% (5). Musculoskeletal pain is common, with chronic joint pain affecting up to 80% of people aged 65 years and older. Cancer also accounts for significant pain in this age group. Other pain syndromes known to affect the geriatric population disproportionately include herpes zoster, temporal arteritis, polymyalgia rheumatica, and atherosclerotic peripheral vascular disease (6). The purpose of this two-part series is to review pathophysiology, significance, and therapeutic interventions for chronic pain; an overview of available treatment strategies also is presented.

DEFINING PAIN

Pain has been defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (7). Pain is classified in many ways, with categories such as good or bad, necessary (requiring no treatment) or unnecessary (requiring treatment), acute or chronic, and organic or psychogenic. "Good" pain is normal and warns of danger (eg, pain from touching a hot stove). In contrast, "bad" pain interferes with the ability to function normally. This article focuses on chronic unnecessary pain.

Acute Pain

Acute pain is defined as pain temporally related to a precipitating event. It is associated with autonomic nervous system hyperactivity, including tachycardia, increased blood pressure, and anxiety. Acute pain often has an observed response that accentuates the painful area by splinting or rubbing and is associated with other behaviors (eg, grimacing). Comprehensive guidelines for acute pain management have been published by the Agency for Health Care Policy and Research and provide an excellent review of the subject (8).

Chronic Pain

In contrast to patients with acute pain, patients with chronic pain may not appear to be in pain and may lack the responses found with acute pain because of an adaptation to sympathetic hyperactivity and anxiety. Objective clinical findings for chronic pain include depression, functional disruptions such as withdrawal from social activities, and personality and lifestyle changes. Therefore, in relation to pain, "chronic" describes not only duration, but a syndrome with specific therapeutic implications. In addition to defining chronic pain as pain that persists for at least 3 months, the International Association for the Study of Pain also includes more than 200 clinical syndromes in the classification of chronic pain (7).

Organic Versus Psychogenic Pain

For pathophysiological reasons, pain is divided into two categories: organic (having an identifiable cause) and psychogenic (lacking an organic cause).

Organic Pain

Organic pain may be nociceptive (associated with potential or ongoing tissue damage) or neuropathic (nervous system dysfunction in the absence of ongoing tissue damage).

Nociceptive pain. Nociceptors are found in cutaneous or deep tissues (somatic) and organs (visceral). Nociceptive pain results from direct stimulation of intact peripheral afferent nerve endings that are sensitive to noxious mechanical, thermal, or chemical stimuli. Chemical mediators of inflammation (eg, bradykinins, prostaglandins) have a central role in the pathogenesis of nociceptive pain. Somatic pain is characterized as constant and easily identifiable and may be described as being aching or throbbing in nature. An example of chronic somatic pain is metastatic bone pain, which is the direct infiltration of bone tissue by malignant cells. This pain may be persistent, diffuse, and unrelated to position or movement, or it may be intermittent, localized, and related to position, weight bearing, or physical activity.

Visceral nociceptive pain tends to be less well localized and is described as dull, dragging, and deep in nature. It is associated with the syndrome of

referred pain, in which the location at which pain is experienced may be different from the pathological source. Examples of visceral pain include back pain from pancreatic or retroperitoneal sources and spasmodic colicky pain caused by organ distention. In general, nociceptive pain responds well to centrally acting analgesics.

Neuropathic pain. Neuropathic pain is caused by injury or disease (as opposed to stimulation) of the nervous system. It may be divided into central or peripheral nervous system disturbance and is designated deafferentation pain. Nervous system injury may result from direct trauma, ischemia (eg, thalamic syndrome), infection (eg, postherpetic neuralgia), metabolic derangement (eg, diabetic neuropathy), or tumor invasion. Neuropathic pain may be constant and steady, or intermittent and lancinating, and is described as burning, shooting, or tingling. Pain may be experienced as abnormal or altered sensations (dysesthesias), paresthesias (electrical shock sensations), hyperalgesia (extreme sensitivity to painful stimuli), or allodynia (pain with touch).

Examples of neuropathic pain include reflex sympathetic dystrophy, phantom limb pain, and postherpetic neuralgia. Response to routine analgesics (including nonsteroidal antiinflammatory drugs [NSAIDs] and centrally acting analgesics) is poor, and adjuvant agents such as corticosteroids, antidepressants, and anticonvulsants are often used. In fact, lack of pain relief from standard opioid doses can be used to screen for neuropathic pain. Nonpharmacological interventions (ablative or augmentative procedures) are often employed to manage neuropathic pain.

Psychogenic Pain

The *Diagnostic and Statistical Manual of Mental Disorders* defines psychogenic pain as a somatoform pain disorder, which is a diagnosis of exclusion (9). Most individuals with somatoform chronic pain believe strongly that their pain is physical and not psychiatric in origin. Because pain is completely subjective, it is as real in this setting as when it is related to any other event or illness, and healthcare providers should realize that the patient is feeling pain.

PSYCHOSOCIAL COMPONENTS OF PAIN

Patients with chronic pain often undergo changes in personality and in ability to function. Furthermor chronic pain may result in symptoms and signs of depression (eg, feelings of hopelessness, weight loss, decreased socialization, sleep disturbance) that can significantly decrease quality of life and increase the need for care. Other complications can include problems with substance abuse (eg, alcohol, illicit drugs) or analgesic addiction. Because of the multiple psychosocial components of pain, a comprehensive treatment program should assess all reasons for pain and their sequelae. By addressing the physical, psychological, social, environmental, spiritual, and financial components of pain, the objective of maintaining meaningful activities can be achieved.

Perception of Pain

Pain is a perception, the result of filtering, modulating, and distorting nociceptive activity in the afferent nervous system through the affective and cognitive processes of the brain. Pain and emotion are closely linked through the activity of sensorineural pathways. As an example, suffering can be viewed as the negative affective state resulting from the interaction of adverse perceptions, such as physical disability, isolation, financial concern, loss of role in the family, and fear of death. Each of these psychological variables can decrease the pain threshold; uncontrolled pain itself may further reduce the threshold. Because the complaint of pain represents the expression of a more global degree of suffering, effective therapy should target more than pain alone.

As part of a pain management program, the pain threshold may be raised by family support, a sense of control, relief of other symptoms, diverting activities, and other positive influences on mood. The meaning of pain to the patient and family and the fears associated with it may be more distressing than the physical suffering itself (10). Addressing and openly discussing these interpretations may reduce the need for other treatment. For example, a patient or family erroneously believing that abdominal pain signals a need for surgery may receive more relief from an explanation than from medication.

Communication Barriers

Inquiring about expectations of pain relief, providing concrete information, communicating confidence in the ability to keep the patient comfortable, and, when appropriate, candidly acknowledging

areas of uncertainty are essential aspects of pain management. This initiative from the physician is especially important because patients may not admit they have pain or may not report pain unless asked. Patients, primarily those who are terminally ill, may refuse offered medication. In some circumstances, patients may be unable to say they are experiencing pain. Nonverbal behavior, such as crying, restlessness, lack of concentration, grimacing, and a gasp or scream when touched (sometimes even when the bed in which a patient is resting is accidentally bumped), may be the only measurements available to assess pain. Preschool-age children often lack the verbal skills needed to describe pain, and older children may not report pain for fear of painful diagnostic evaluations. As in adults, nonverbal behavioral manifestations may be the only clues to the existence of pain in children.

Social Issues

The social value of suffering also must be addressed. A person may hate his job and as a result of pain cannot work; loss of disability, pension, and benefits if pain subsides are powerful unconscious incentives to maintain pain. Pain may be provided as an excuse for failure in relationships, and certain patients may perceive pain as necessary to receive attention from their family or physician. Psychiatric consultation may be indicated when extreme forms of manipulation occur, almost always as part of a lifelong pattern (10).

NEURAL PATHWAYS IN CHRONIC PAIN

Pain sensation in the peripheral nervous system depends on nerve receptors (ie, nociceptors), some of which have yet to be defined. These receptors generate signals that are transmitted along myelinated or unmyelinated nerve fibers. Small-diameter, myelinated, Aδ-nociceptive afferent nerves rapidly transmit (milliseconds to seconds) pain signals that are experienced as sharp pain. Unmyelinated C primary afferent nerve fibers convey signals more slowly and produce a slow-building, dull, or burning pain. Eighty percent of fibers in peripheral nerves are unmyelinated, and more than 90% of those are nociceptive.

Pain Transmission

The major neural pathways involved in the perception of pain are summarized in Figure 1.

Peripheral afferent fibers arise from cell bodies in the dorsal root ganglion. These cell bodies send central projections to the dorsal horn of the spinal cord and synapse on projection neurons that integrate and carry pain signals to higher central nervous system (CNS) structures. Projection neurons traverse the spinothalamic tract to the reticular and sensory nuclei of the thalamus, which project onto discrete somatosensory regions within the postcentral parietal cortex. Further processing of the nociceptive input involves the cerebral cortex. Although its role is not fully understood, the cerebral cortex is fundamental to the perception of pain.

The thalamus is important in the transmission of the sensory and discriminative aspects of pain (ie, intensity), whereas the intralaminar nuclei play a role in the affective-motivational aspects of pain (12). There is active communication between these pathways; 15% to 20% of spinothalamic tract fibers branch to both intralaminar and lateral thalamic nuclei. The spinothalamic tract also projects numerous collaterals to brainstem structures (eg, periaqueductal reticular formation), and secondary relays from the midbrain periaqueductal gray and reticular formation converge back into the intralaminar nuclei (12).

The efferent nerves of the pain modulation pathway pass through the spinal cord in the dorsolateral funiculus and terminate at nociceptive sensory projection neurons in the dorsal horn of the spinal cord. The information reaching the dorsal horn of the spinal cord is also subject to modulation by local circuit neurons. Interestingly, nonnociceptor peripheral afferent nerves conveying touch sensation also synapse on the same projection neurons as nociceptive peripheral afferent fibers. Signals from nonnoxious stimuli can prevent the transmission of painful stimuli by inhibiting the pain projection neurons of the dorsal horn.

Chemical Mediators

Most nociceptive fibers are self-activated by the release of neurotransmitters; however, substances released from tissue damage at the site of injury (eg, histamine, bradykinin, leukotrienes) also can cause activation (12). Examples of other neurotransmitters contained in primary afferent nerves include somatostatin, calcitonin gene–related peptide, and substance P. Substances involved in pain modulation (ie, neuromodulators) in the CNS in-

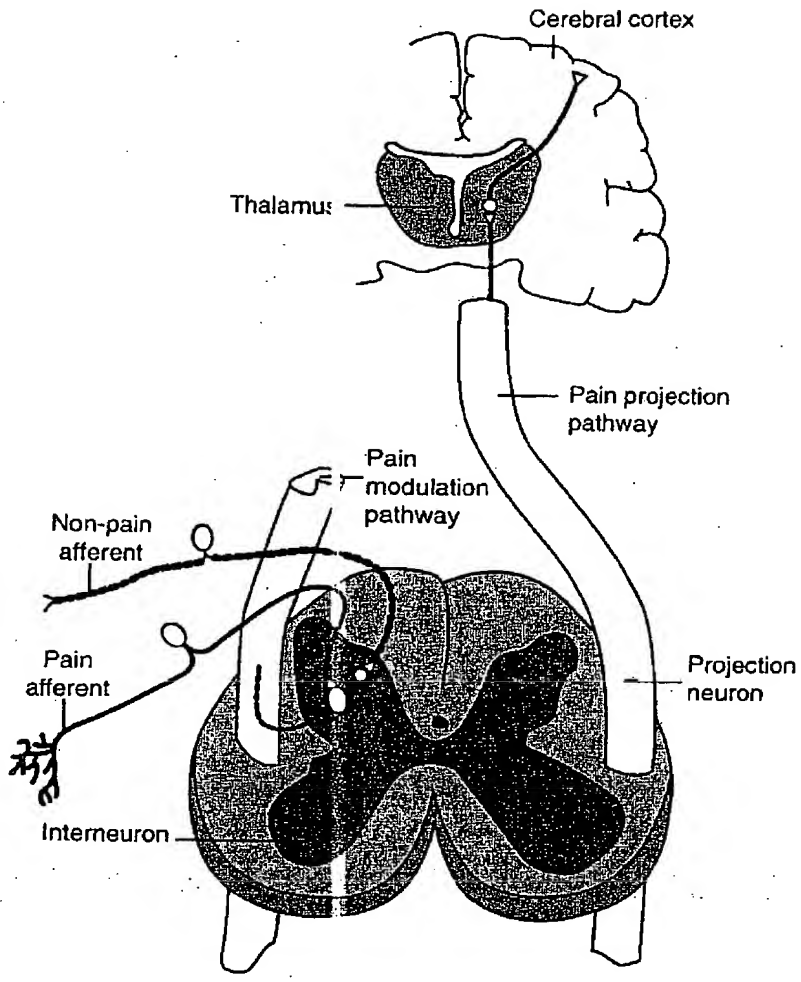

Fig 1. Pain transmission and modulation pathways. Afferent fibers transmit painful stimuli to interneurons located in the dorsal horn, where the signals are relayed to projection neurons leading up the spinal cord into the thalamus and cerebral cortex. Pain modulation pathways descend from the brainstem through the spinal cord to the interneuron level. (Reprinted with permission of the American College of Physicians [11].)

clude the enkephalins and endorphins. The biogenic monoamines norepinephrine and 5-hydroxytryptamine (serotonin) are also considered neuromodulators, regulating nerve transmission in the descending pain pathways that originate in the medullary reticular formation (12). In some patients with chronic organic pain syndromes, enkephalin and serotonin metabolites are present in reduced concentrations in the cerebrospinal fluid (13). A number of other chemical mediators are known to be released from sensory nerve endings, but their role in chronic pain syndromes has not been well defined.

Substance P, which appears to be the principal sensory mediator of pain, activates C-fiber nociceptors (14). It also mediates pain at the central nerve terminal of primary afferent nerves in the dorsal horn (15). In some chronic pain syndromes, such as fibromyalgia, substance P is found in the cerebrospinal fluid in increased concentrations, implying a role in the pathophysiology of chronic pain states (16). However, other studies report low levels of substance P in chronic pain syndromes (13).

Hyperalgesia

Hyperalgesia refers to the state of increased sensitivity to painful stimuli resulting from an alteration in the normal pain threshold of a particular tissue. Primary hyperalgesia refers to the occurrence of these changes at the site of injury, whereas secondary hyperalgesia refers to changes in the pain threshold occurring in tissues surrounding an